Safety Assessment of HC Yellow No. 5

March 16, 2004

The 2004 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This final safety assessment was prepared by Sonal V. Iyer, former CIR Scientific Analyst and Writer, and Dina M. Benes, CIR Scientific Analyst and Writer.
Final Report on the Safety Assessment of HC Yellow No.5

Abstract: 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 which is evaluated at 48 hours 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 LD₅₀ 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 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 non-mutagenic and non-cytotoxic in standard laboratory assays. A current review of the hair dye epidemiology literature identified that use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of an association with cancer or other adverse events. The Panel recognizes that hair dye epidemiology studies do not address the safety of individual hair dyes. Based on the available safety test data on HC Yellow No.5, the Panel determined that this ingredient would not likely have carcinogenic potential as used in hair dyes. 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.

INTRODUCTION

HC Yellow No. 5 is a direct hair dye. The following report is a summary of the safety data in this cosmetic ingredient.

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 below:

![Chemical Structure of HC Yellow No. 5]

Synonyms listed in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and McEwen, 2004) include:

- 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,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
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- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
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- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
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- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
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- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
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- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
- N1-(2-Hydroxyethyl)-4-Nitro-o-Phenylenediamine,
PHYSICAL AND CHEMICAL PROPERTIES

The limited data available on the chemical and physical properties of HC Yellow No. 5 are given in Table 1.

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 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).

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 2 (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 - 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 semi-permanent dyes. Such dyes are non-oxidative. 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. Under normal conditions of use, skin contact with hair dye is restricted to 30 minutes.

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).*

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### Table 1. Chemical and Physical Properties (Keystone Aniline Corp. 2002)

<table>
<thead>
<tr>
<th>Description</th>
<th>Molecular Weight</th>
<th>Empirical Formula</th>
<th>Solubility</th>
<th>Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellow to orange crystal or powder</td>
<td>197.19</td>
<td>C₂H₁₂N₂O₂</td>
<td>Slightly soluble in water and alcohol at 25°C and 60°C</td>
<td>132 °C</td>
</tr>
</tbody>
</table>
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 which is evaluated at 48 hours after application of the test material.

The hair dye HC Yellow No. 5 is not prohibited in cosmetic products that are marketed in Japan (MHLW, 2001). In the European Union there have been no restrictions on HC Yellow No. 5 (European Union On-Line, 2000).

NON-COSMETIC

No information was found on non-cosmetic uses for HC Yellow No. 5.

BIOLOGICAL PROPERTIES

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

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

HC Yellow No. 5 (1.875% unlabelled and 1.125% ¹¹C-labelled) in aqueous solution, that appeared to mimic a hair dye product, was applied using a spatula to a 3 cm² area of the clipped dorsal skin on Sprague Dawley rats. Animals were restrained during the 30 minute 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 hours and then killed. Urine and feces were collected over each of three 24 hour 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 3 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). 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.

### Table 2. Frequency of Use of HC Yellow No. 5

<table>
<thead>
<tr>
<th>Product category</th>
<th>Number of formulations containing HC Yellow No. 5 (FDA, 2002)</th>
<th>Concentration of use (%) (CTFA, 2003)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair dyes and colors (1690)</td>
<td>32</td>
<td>1.6</td>
</tr>
<tr>
<td>Hair tints (49)</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>Total uses of HC Yellow No.5</td>
<td>37</td>
<td>0.2 - 1.6</td>
</tr>
</tbody>
</table>
Table 3. Percentage distribution of radioactive label in rats exposed to HC Yellow No. 5  
(Österreichisches Forschungszentrum Seibersdorf GmbH, 1997)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hair dye alone</th>
<th></th>
<th>Hair dye plus developer</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>rinse water</td>
<td>95.6</td>
<td>2.3</td>
<td>94.3</td>
<td>0.83</td>
</tr>
<tr>
<td>hair stubs</td>
<td>1.45</td>
<td>0.63</td>
<td>2.70</td>
<td>0.54</td>
</tr>
<tr>
<td>stratum corneum</td>
<td>0.048</td>
<td>0.023</td>
<td>0.098</td>
<td>0.016</td>
</tr>
<tr>
<td>epidermis/dermis</td>
<td>0.0248</td>
<td>0.0073</td>
<td>0.075</td>
<td>0.035</td>
</tr>
<tr>
<td>percutaneous penetration</td>
<td>0.054</td>
<td>0.013</td>
<td>0.124</td>
<td>0.046</td>
</tr>
<tr>
<td>urine as a function of time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 24 hours</td>
<td>0.028</td>
<td>0.010</td>
<td>0.067</td>
<td>0.045</td>
</tr>
<tr>
<td>24 - 48 hours</td>
<td>0.00682</td>
<td>0.00096</td>
<td>0.0126</td>
<td>0.0049</td>
</tr>
<tr>
<td>48 - 72 hours</td>
<td>0.00277</td>
<td>0.00071</td>
<td>0.0047</td>
<td>0.0022</td>
</tr>
<tr>
<td>total excreted in urine</td>
<td>0.037</td>
<td>0.011</td>
<td>0.084</td>
<td>0.045</td>
</tr>
<tr>
<td>feces as a function of time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 24 hours</td>
<td>0.0081</td>
<td>0.0041</td>
<td>0.0171</td>
<td>0.0089</td>
</tr>
<tr>
<td>24 - 48 hours</td>
<td>0.0051</td>
<td>0.0022</td>
<td>0.0151</td>
<td>0.0070</td>
</tr>
<tr>
<td>48 - 72 hours</td>
<td>0.0025</td>
<td>0.0011</td>
<td>0.0042</td>
<td>0.0011</td>
</tr>
<tr>
<td>total excreted in feces</td>
<td>0.0157</td>
<td>0.0029</td>
<td>0.0364</td>
<td>0.0098</td>
</tr>
<tr>
<td>organs/carcass</td>
<td>0.0011</td>
<td>0.00023</td>
<td>0.0029</td>
<td>0.0014</td>
</tr>
<tr>
<td>Total recovery</td>
<td><strong>97.2</strong></td>
<td><strong>2.2</strong></td>
<td><strong>97.3</strong></td>
<td><strong>0.81</strong></td>
</tr>
</tbody>
</table>

Excretion of the very small absorbed amount was approximately 70% urine and 30% feces in both groups. Most of the urinary excretion (75 - 80%) occurred in the first 24 hours (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% in water) using WISW strain rats. Two male rats (157.9 - 184.1 g) and two female rats (147.7 - 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 average LD$_{50}$ for both sexes was calculated to be 555.56 mg/kg, but LD$_{50}$ for females appeared lowered than that of males.

**CHRONIC ORAL TOXICITY**

Wernick et al. (1975) performed a chronic toxicity test on eighteen male and eighteen female purebred Beagle dogs. The animals, 6-8 months of age, were divided into three groups of six males and six females. A composite material representative of commercially available semi-permanent 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 4.

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 six, twelve, and eighteen months and on all survivors at twenty-four months. No significant effects were observed. Urine was blue black and returned to normal color after overnight fasting. No change in urinalysis was seen with the blue black urine.

**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 hours after application, sites were read for erythema and edema. One rabbit had erythema on both sites at 24 hours, but it disappeared by 72
Table 4. Dye/Base Composite (Wernick et al., 1975)

<table>
<thead>
<tr>
<th>CTFA dictionary name</th>
<th>Chemical abstract name/dye type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Orange 3</td>
<td>Sodium 4-anilino-2',4'-dinitrodiarylamine-sulfonate</td>
<td>0.24</td>
</tr>
<tr>
<td>HC Blue No. 2</td>
<td>2,2'-(4-[2-Hydroxyethylamino]-3-nitrophenyl)iminodiethanol</td>
<td>1.63</td>
</tr>
<tr>
<td>Celliton Fast Navy Blue BRA¹</td>
<td>-</td>
<td>0.64</td>
</tr>
<tr>
<td>2-Nitro-β-phenylenediamine</td>
<td>1,4-Diamino-nitrobenzene</td>
<td>0.24</td>
</tr>
<tr>
<td>4-Nitro-α-phenylenediamine</td>
<td>1,2-Diamino-4-nitrobenzene</td>
<td>0.16</td>
</tr>
<tr>
<td>2-Amino-4-nitrophenol</td>
<td>2-Amino-4-nitrophenol</td>
<td>0.05</td>
</tr>
<tr>
<td>HC Yellow No. 5</td>
<td>2-[2-Amino-4-nitroanilino]ethanol</td>
<td>0.05</td>
</tr>
<tr>
<td>HC Yellow No. 4</td>
<td>2,2'-(2-Hydroxy-4-nitrophenyl)-iminodiethanol</td>
<td>0.31</td>
</tr>
<tr>
<td>Disperse Violet 11</td>
<td>-Anthraquinone</td>
<td>0.40</td>
</tr>
<tr>
<td>Disperse Blue 1</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Disperse Black 9</td>
<td>-Diazo</td>
<td>0.13</td>
</tr>
<tr>
<td>HC Blue No. 1</td>
<td>2,2'-(4-Methylamino)-3nitrophenyliminodiethanol</td>
<td>1.54</td>
</tr>
<tr>
<td>HC Red No. 3</td>
<td>2-[4-Amino-2-nitroanilino]ethanol</td>
<td>0.02</td>
</tr>
<tr>
<td>HC Yellow No. 3</td>
<td>2-bis(Hydroxymethyl)-2-[2-amino-4-nitroanilino]ethanol</td>
<td>0.65</td>
</tr>
<tr>
<td>HC Yellow No. 2</td>
<td>2-[2-Nitroanilino]ethanol</td>
<td>0.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CTFA dictionary name</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauramide DEA</td>
<td>20.22</td>
</tr>
<tr>
<td>Imino-bis propylamine</td>
<td>9.64</td>
</tr>
<tr>
<td>Cellulose ether</td>
<td>17.94</td>
</tr>
<tr>
<td>Citric acid</td>
<td>16.02</td>
</tr>
<tr>
<td>BHT</td>
<td>1.61</td>
</tr>
<tr>
<td>Sodium m-nitrobenzenesulfonate</td>
<td>2.25</td>
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<tr>
<td>TEA-Dodecylbenzene sulfonate</td>
<td>1.61</td>
</tr>
<tr>
<td>Monoethanolamine</td>
<td>22.42</td>
</tr>
<tr>
<td>Perfume</td>
<td>0.67</td>
</tr>
<tr>
<td>Perfume</td>
<td>0.67</td>
</tr>
</tbody>
</table>

¹ A mixture of: Disperse Yellow 1–2,4-Dinitro-4'-hydroxydiphenylamine; Disperse Blue 1–1,4,5,8-Tetraaminoanthraquinone; Disperse Violet 4–1-Amino-4'-methylaminoanthraquinone; and Disperse Red 17–4-(bis-hydroxyethyl)amino-2-methyl-4'-nitrobenzene

hours. Another rabbit had erythema at 24 hours only at the shaved site and this disappeared at 72 hours. 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 eight hours later, the animals received the test (1%), positive control (0.025%), and negative control (1%) materials dermally in petrolatum (0.5
The next day (48 hours 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 were exposed to decreasing concentrations of the test material (1, 0.5, and 0.25%) and D NCB (0.1, 0.05, and 0.025%) in water, or water alone in Hill Top chambers. At 24 hours, the chambers were removed and the animals observed. Animals were also observed at 48 hours. No irritation reactions were reported to HC Yellow No. 5 in the exposed or negative control groups at 24 or 48 hours. The positive control at 0.1% produced sensitization reactions in 10/10 animals at 24 and 48 hours; 0.05% produced sensitization reactions in 8/10 animals at 24 and 48 hours; and 0.025% produced sensitization reactions in 4/10 animals at 24 and 48 hours. (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 seconds before rinsing. In three animals, the test material was allowed to stay in the eye for 30 seconds before rinsing. In three animals, the eye was not rinsed. Animals were observed for seven 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 strain rats. Sixty males and 120 females were divided into six groups of ten males and twenty 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. Part I, the females received the basal diet from eight weeks prior to mating through weaning. The males used to breed the females were fed the test diets for eight weeks prior to mating and during the mating period. In Part II, males received the basal diet for eight weeks prior to and during mating, while the females received the test diets eight weeks prior to mating, during gestation, and twenty-one 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.

A teratology study was performed by Wernick et al. (1975) on thirty male and sixty female virgin CFE-S 15-week-old rats using the composite of dyes listed in Table 4 given in feed. The rats were divided into three groups of twenty. The composite was placed in the feed at six to day fifteen 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 one of the thirteen pups in the high dose group. In the litter with the abnormal pup, there were twelve other pups that were normal. The rats in the teratology and reproductive studies excreted blue-brown urine.

Wernick et al. (1975) performed a teratology study on forty-eight sexually mature female New Zealand White rabbits. The rabbits were artificially inseminated and placed into four groups of twelve rabbits. The rabbits received, by oral gavage, the composite mixture in Table 4 on days six to eighteen 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.

A study by DiNardo JC et al. (1985) examined the teratology of HC Yellow No. 5 using Sprague-Dawley rats. Ten to thirteen pregnant rats received, by oral gavage, the dye on gestation days six through fifteen. 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 - 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 - 6, 6 - 11, 11 - 16, and 16 - 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 was 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 non-skeletal 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 sterna 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; and
- less than 4 completely ossified sterna 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;
- 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 5 presents a summary of HC Yellow No. 5 genotoxicity studies.

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 S-9. 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 S-9 induction specific. Without S-9, sodium azide (SA) was used with TA1535 and TA100, 9-aminoacridine (9AA) with TA1537, and 2-nitrofluorene (2NF) with TA98. With S-9 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 revertant 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).

This laboratory also conducted a mouse micronucleus test on HC Yellow No. 5 (Hans Schwartzkopf GmbH, 1985b). 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 hours, 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 ten animals received cyclophosphamide at 40 mg/kg and was killed at 24 hours. Polychromatic erythrocytes (1000 where possible) were counted for each animal.

While many animals (mostly males) yielded poorly distributed micronuclei or were simply uncountable, statistical analyses
Table 5. HC Yellow No. 5 Genotoxicity Studies

<table>
<thead>
<tr>
<th>Test system</th>
<th>HC Yellow No. 5 Concentration or dose</th>
<th>Number of animals</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. typhimurium TA 1535, TA 1537, TA 98, TA 100</td>
<td>8, 40, 200, 1000, 5000 μg/plate</td>
<td>-</td>
<td>Concentration dependent increase in number of revertants per plate, with or without metabolic activation frameshift mutations speculated</td>
<td>Hans Schwartzkopf GmbH, 1985a</td>
</tr>
<tr>
<td>Mouse micronucleus test</td>
<td>240 mg/kg</td>
<td>3 groups of 5 male and 5 females</td>
<td>No statistically significant effect</td>
<td>Hans Schwartzkopf GmbH, 1985b</td>
</tr>
<tr>
<td>Mouse micronucleus test</td>
<td>150 mg/kg</td>
<td>3 groups of 5 male and 5 females</td>
<td>No cytotoxic or mutagenic effects noted</td>
<td>Österreichisches Forschungszentrum Seibersdorf GmbH, 1988</td>
</tr>
<tr>
<td>Mutation assay in mouse lymphoma cells</td>
<td>0.46, 1.37, 4.11, 12.3, 37.0, 111.1, 333.3, and 1000 μg/ml</td>
<td>-</td>
<td>No statistically significant increase in resistant cells with or without metabolic activation</td>
<td>Labor L+S GmbH, 1989</td>
</tr>
<tr>
<td>Chromosome aberration in human peripheral blood lymphocytes</td>
<td>30, 100, and 300 μg/ml</td>
<td>-</td>
<td>No significant increase in number of aberration with or without metabolic activation, highest concentration 50% cytotoxic</td>
<td>King &amp; Harnasch GmbH, 1990</td>
</tr>
<tr>
<td>Genotoxicity assay in Chinese hamster cells</td>
<td>78.1, 156, 313, 625, 1250, 1500, 1750, 2000, 2250 μg/ml</td>
<td>-</td>
<td>No significant increase in mutants with or without metabolic activation, however concentrations above 1500 μg/ml were cytotoxic in concentration dependent manner</td>
<td>Research Toxicology Centre S.p.A. (1996)</td>
</tr>
</tbody>
</table>

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 5 male and 5 female Crl:NMRI BR mice received a single dose. Animals were killed at 24, 48, and 72 hours. A negative control group received the vehicle only and was killed at 48 hours. A positive control group received cyclophosphamide and was killed at 24 hours.

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

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).

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 S-9 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.

The 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 were 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 S-9 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 hours in complete medium, cell cultures were exposed to the test material for 24 hours 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 S-9. After 2 hours at 37 °C, the cells were again centrifuged, washed, and resuspended in complete medium. Incubation continued to 24 hours.

Positive control exposures produced the expected increase in chromosome aberrations (gaps, chromosome deletions/exchanges, chromatid deletions/exchanges, isolocus deletions). While 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 cell 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 S-9 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).

**CARCINOGENICITY**

No information was found 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.

**EPIDEMIOLOGY DATA**

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, while direct hair dyes are a preformed color. HC Yellow No. 5 is a direct hair dye.

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, 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 authors concluded that the available evidence is insufficient to conclude a causal association between personal hair dye use and bladder cancer, non-Hodgkin’s lymphoma, and multiple myeloma. With respect to other cancers, including leukemia, breast cancer, or childhood cancers, and autoimmune disease or adverse developmental/reproductive effects, the authors concluded that the evidence also did not demonstrate a causal association with hair dye use.
A case-control study (Gago-Dominguez et al. 2001, 2003) described in the 2003 review, did suggest a possible genetically susceptible subgroup, which detoxify 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. The review authors noted that these results were based on small sample sizes.

The 2003 review authors recommended the replication of studies to better understand the observed associations, but concluded that the available information is insufficient to conclude the association between personal hair dye use and the health outcomes discussed is causal. The Panel also considered two additional case-control studies that examined the relationship of hair dye use or diet with non-Hodgkin’s lymphoma (Zhang, et al. 2004; Zheng, et al. 2004).

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, while not the focus in all investigations, appear 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 which is evaluated at 48 hours after application of the test material.

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

The oral LD₅₀ 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 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 non-mutagenic and non-cytotoxic in standard laboratory assays. Direct hair dyes, while not the focus in all epidemiology studies, appear to have little evidence of an association with cancer or other adverse events.

**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 which is evaluated at 48 hours 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. While there were no data available on the carcinogenic effect of HC Yellow No. 5, the Panel noted that, in several bacterial and 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, 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. Direct hair dyes, while 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.

**REFERENCES**


Food and Drug Administration (FDA). 1976. Cosmetic Product Warning Statements: coal tar hair dyes containing 4-methoxy-m-phenylenediamine (2,4-diaminooanisole) or 4-methoxy-m-phenylenediamine sulfate (2,4-diaminoanisole sulfate). *Federal Register* 44(201):59509-10.


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1 Available from the Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036
