

Public Citizen

Congress Watch • Critical Mass Energy Project • Health Research Group • Litigation Group • Tax Reform Group

December 17, 1984

Frank D. Young, M.D., Ph.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD. 20857

Dear Dr. Young,

Public Citizen Health Research Group petitions you to ban ten widely-used food, drug or cosmetic dyes, all of which have been shown to cause cancer. None of these dyes has ever been found safe by FDA for all uses but all have remained on the market pending resolution of their "provisionally listed" status.[1] For six of the ten dyes, FDA recommended such a ban nine months ago.[2] Three of the ten dyes are food dyes (Yellow 5, Yellow 6 and Red 3) with 1984 consumption of 3.4 million pounds, comprising over half of all food dyes consumed in the United States that year. As long as these dyes remain on the market, FDA is violating the safety requirements of the Color Additive Amendments to the Food, Drug and Cosmetic Act, 21 U.S.C. Section 376. In addition, by delaying a final decision, the agency has violated the transitional provisions of the Color Additives Amendments, and the Administrative Procedure Act which prohibits agency action "unreasonably delayed", 5 U.S.C. Section 706(1). By failing to immediately ban these dyes, the Reagan Administration is making a mockery out of its alleged cancer reduction goals and is completely demoralizing dozens of FDA employees who know these dyes are too dangerous for continued use by the public. In the past several years, after receipt by FDA of animal studies showing each of those ten dyes to be carcinogenic, Americans have ingested (food and drug dyes) or rubbed on themselves (cosmetics dyes) over 6.6 million pounds of these cancer-causing dyes.

1. The 1960 Color Additive Amendments, requiring all permanently listed dyes to be proven safe, provided for a provisional list of dyes already on the market which could be marketed for 2 1/2 years or longer pending the completion of scientific studies to prove safety. These 10 dyes have been on the provisional list for more than 20 years because FDA has repeatedly extended their provisional status.

2. Letter, March 30, 1984 from Acting FDA Commissioner Dr. Mark Novitch to HHS Secretary Margaret Heckler.

The chart on the next page (Table 1) lists the dyes, their uses, the number of pounds certified by FDA after the dyes were found to be carcinogenic, and the major types of toxicity including type of tumor for each dye. (Attachment A gives further details on these ten dyes.)

We have obtained a copy of an internal FDA memo confirming the illegality of marketing five of these dyes (D&C Reds 8, 9, 19, and 37 and D&C Orange 17) written to you by FDA's Director of the Center for Food Safety and Applied Nutrition Dr. Sanford Miller on November 23, 1984. Dr. Miller, referring to the cosmetic industry's plea for further review of the dyes, said:

In other words, the only effect that we can realistically see from additional peer review is a further delay that would risk a lawsuit asserting that FDA is not adhering to its responsibilities under the law. In our judgment we have already extended the provisional list so many times for such tenuous reasons that we are in danger of losing both a lawsuit and our credibility as a regulatory agency. In addition, an adverse court ruling on the provisional list could also adversely affect the status of the other provisionally listed color additives that have not been shown to be carcinogens but face questions that still need resolution.

At a Congressional hearing on October 5, 1984 you indicated that FDA would ban these five dyes, but now, 2 1/2 months later, they are still being used and FDA has again extended their provisional status to February, 1985.

HISTORY OF FOOD DYES

Although we are very concerned about any carcinogenic or otherwise toxic dye, food dyes are the biggest worry because much larger quantities of these dyes are produced and ingested and because, as will be discussed in the next section, children are major targets/victims of food dyes.

The history of food dyes in the United States is really a history of disappearing food dyes. Of the 24 food dyes which at one time have been allowed in the American food supply, 17 are now banned, delisted or no longer produced as can be seen in the top part of Table 2 on page 4.

Of the seven food dyes still used (see bottom part of Table 2), three (Red 3, Yellow 5 and Yellow 6) are the subject of today's petition. These three alone, however, accounted for 3,396,855 pounds or 53% of all food dyes certified in fiscal 1984. The other four dyes also have serious questions about their safety as indicated in the bottom part of Table 2. Of these four, Blue 2 is currently the subject of an FDA Administrative Hearing as a result of Public Citizen's objections to the

TABLE 1:

10 FOOD, DRUG, OR COSMETIC DYES WHICH
PUBLIC CITIZEN HEALTH RESEARCH GROUP IS ASKING FDA TO BAN

<u>Dye</u>	<u>Uses</u>	<u>Pounds Certified Since Studies Completed</u>	<u>Toxicity Findings</u>	<u>Comments</u>
FD&C Red 3	Food and Drugs (candy, desserts, baked goods)	705,496 (1983-4)	Thyroid tumors, Chromosomal damage	FDA proposed a ban
FD&C Yellow 5	Food, Drugs and Cosmetics (pet food, bever- ages, baked goods)	3,091,155 (1983-4)	Allergy, thyroid tu- mors, lymphocytic lym- phoma, chromosomal damage	Banned in Norway Contains known human carcinogens
FD&C Yellow 6	Predominantly Food (beverages, candy, desserts)	2,621,631 (1983-4)	Kidney tumors, allergy, chromo- somal damage	Banned in Norway, Sweden; contains known human carcino- gens.
D&C Red 8	Ingested Drugs and Cosmetics	3,323 (1982-4)	Splenic tumors	FDA proposed a ban
D&C Red 9	Ingested Drugs and Cosmetics	126,148 (1982-4)	Splenic tumors	FDA proposed a ban
D&C Red 33	Ingested Drugs and Cosmetics	28,218 (1983-4)	Splenic tumors	"Potential to be a carcinogen" (FDA)
D&C Orange 17	Drugs and Cosmetics	9,388 (1983-4)	Liver tumors	FDA proposed a ban
D&C Red 19	Drugs and Cosmetics	26,830 (1982-4)	Thyroid, parathyroid and brain tumors	FDA proposed a ban
D&C Red 37	Drugs and Cosmetics	0	Thyroid, parathyroid and brain tumors	FDA proposed a ban
D&C Red 36	Drugs and Cosmetics	6,413 <u>(1984)</u>	Breast tumors	

TOTAL: 6,619,602 Pounds

TABLE 2:

DISAPPEARING FOOD DYES: 17 GONE - MORE TO GO17 U.S. FOOD DYES NOW BANNED, DELISTED OR NOT PRODUCED

<u>DYE</u>	<u>YEAR BANNED, DELISTED (OR LAST PRODUCED)*</u>
SUDAN 1	1918
BUTTER YELLOW	1918
RED 32	1956
ORANGE 1	1956
ORANGE 2	1956
YELLOW 1	1959
YELLOW 2	1959
YELLOW 3	1959
YELLOW 4	1959
RED 1	1961
GREEN 1	1966
GREEN 2	1966
VIOLET 1	1973
RED 2	1976
RED 4	1976
CITRUS RED 2	1976*
ORANGE B	1978*

7 REMAINING FOOD DYES IN U.S.

<u>DYE</u>	<u>MAIN USES</u>	<u>POUNDS CERTIFIED 1984</u>	<u>TOXICITY FINDINGS</u>	<u>COMMENTS</u>
RED 3	Candy, Desserts, Baked goods	241,265	Thyroid tumors, chromosomal damage	FDA Recommended Ban
RED 40	Beverages, Candy, Desserts, Pet Food	2,630,578	Earlier lymphomas (lymph tumors)	Banned in EEC
BLUE 1	Beverages, Candy, Baked Goods	260,417	Chromosomal damage	Banned in France, Finland
BLUE 2	Pet Foods, Candy, Beverages	101,223	Brain tumors	Banned in Norway (pending FDA hearing)
GREEN 3	Beverages, Candy	3,597	Bladder tumors	Banned in EEC
YELLOW 5	Pet Food, Beverages, Baked Goods	1,620,540	Allergies, thyroid tumors, lymphocytic lymphomas, chromoso- mal damage	Banned in Norway
YELLOW 6	Beverages, Candy, Desserts, sausage	1,535,050	Allergies, Kidney tumors, chromosomal damage	Banned in Norway, Sweden

TOTAL: 6,392,670 Pounds

FDA's decision to permanently list it. There was a statistically significant increased number of brain tumors in animals fed Blue 2. We are currently receiving the safety studies on the other three dyes (Green 3, Red 40 and Blue 1) because of the toxic findings listed in Table 2.

It is likely that in a very short time, there will be few, if any "certified" petroleum-derived food dyes left. Fortunately, products such as Dannon Yogurt ("No artificial anything"), General Foods' Cheerios (no Yellow 5 as in the past), and many others have shown, by their extraordinary success, that we can all do very well without these dyes.

CHILDREN AND FOOD DYES

In July 1976, the FDA Division of Consumer Studies published a report concerning the ingestion of food dyes by children in the United States. Some of their findings were the following:

- * 95 - 99% of children eat some food containing coal-tar (petroleum derived) food dyes.
- * Over four million children will have consumed a total of more than one pound of coal-tar food dyes by the time they are 12 years old.
- * The maximum consumption of food dyes by children is as high as three pounds by age 12.

These figures are quite conservative since there has been a 50% increase in the total use of food dyes in the past ten years.

In addition to the possibility that they are more susceptible to carcinogenic chemicals such as food dyes, children will have a longer history of ingestion and thus a greater likelihood of developing cancer because they eat these dyes.

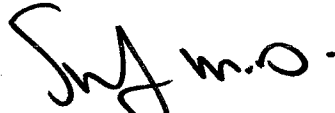
SUMMARY

It is time to finally reject the food industry-influenced 1971 National Academy of Sciences' Committee on Food Protection contrived rationalization of the need for food dyes from the introduction of their report Food Colors:

Certain foods have been artificially colored for many years, and we have come to expect them to have a characteristic color intensity and hue. Those that do not are often considered unacceptable, however wholesome they may be. And we have come to assume that such foods as beverages and fruit drinks, gelatin desserts, maraschino cherries, candied fruits, jellies, candies and other confections, ice cream, sherberts, breakfast cereals, bakery goods, snack foods and pet foods will be appropriately colored.

If you do not promptly act on our petition, we will be forced to initiate legal action. As your own FDA official, Dr. Sanford Miller, Director of the Center for Food Safety and Applied Nutrition, has stated, if five of these ten dyes are not banned, "we have already extended the provisional list so many times for such tenuous reasons that we are in danger of losing both a lawsuit and our credibility as a regulatory agency". We agree.

Sincerely,

A handwritten signature in cursive script that reads "Sidney M. Wolfe, M.D.".

Sidney M. Wolfe, M.D.
Director

A handwritten signature in cursive script that reads "Peter Lurie".

Peter Lurie
Staff Researcher

ATTACHMENT A
LISTING OF COLOR ADDITIVES

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FD&C Red No. 3.1
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D&C Orange No. 17.11
D&C Red No. 1913
D&C Red No. 3713
D&C Red No. 3615

Dye: FD&C Red No. 3 (Erythrosine)

Major Uses: Predominantly food (candy, baked goods, dessert powders), but also in pharmaceuticals.¹

Pounds certified by FDA:²

1982: 420,873

1983: 464,231

1984: 241,265

Current Status: Provisionally listed for use in cosmetics and externally applied drugs; lake provisionally listed for use in food and ingested drugs; salt permanently listed for use in food and ingested drugs.

No. of extensions of provisional listing since February, 1981: 9

Summary of evidence against permanent listing:

Over 2 years have elapsed since the completion of chronic feeding studies in rats and mice. The results of those studies and others are as follows:

--1982 long-term rat feeding study³ (dose: 4.0%) found:

- a. statistically significant increase in follicular adenomas of the thyroid in males.
- b. statistically significant increase in thyroid follicular hyperplasia/cysts in males.
- c. increased incidence of thyroid C-cell adenomas in males.
- d. slight to moderate decreases in mean body weights for males and females.

The study report concluded: "The compound was oncogenic for thyroid follicular tumors for males of this species and strain under the conditions of this study."⁴

--1981 long-term mouse feeding study⁵ (doses: 0.3%, 1.0%, 3.0%) found:

- a. statistically significant increase in lymphocytic lymphoma in low dose males.
- b. statistically significant decreases in body weight in males and females in the high dose group.

--1983 endocrine study of FD&C Red No. 3 concluded: "The present study clearly demonstrates that feeding of FD&C Red #3 at a level of 4 percent in the diet produces an endocrine state of hyperthyroidism."⁶

--Two studies cited by the World Health Organization showed a slight but statistically significant mutagenic effect for FD&C Red No. 3 in bacterial studies.⁷

--FD&C Red No. 3 has been found to induce chromosomal damage in Chinese hamster fibroblast cell lines.⁸

--1976 FDA study in gerbils showed that FD&C Red No. 3 "produced a dose-related change in the thyroid reminiscent of human nodular goitre."⁹

The FDA has recognized the carcinogenicity of FD&C Red No. 3, noting, on October 4, 1983, "a treatment-related occurrence of thyroid follicular adenomas when FD&C Red No. 3 was administered in the animals' diet."¹⁰ In extending again the provisional listing of FD&C Red No. 3 in the same issue of the Federal Register, FDA stated: "The agency wishes to

emphasize that the sole purpose of this extension is to obtain the views of the National Toxicology Program [NTP] on existing data. Based on the existing data and the National Toxicology Program's scientific evaluation, FDA will proceed promptly to normalize the regulatory status of FD&C Red No. 3 in accordance with its judgment about whether the data show that the color additive is 'safe'¹¹. On October 27, 1983 the NTP Peer Review Panel met and noted "convincing evidence of carcinogenicity for FD&C Red No. 3 in male rats."¹² Thus, 9 months have elapsed since the NTP report without any action by the FDA. Perhaps this is attributable to the 30 members of the House of Representatives¹³ and the 8 Senators¹⁴ who have written to the Secretary of Health and Human Services, Margaret M. Heckler, attempting to prevent FD&C Red No. 3 from being banned.

Footnotes for FD&C Red No. 3

1. National Academy of Sciences, "Food Colors," Washington, D.C., 1971.
2. Division of Color Technology, Certification Branch.
3. International Research and Development Corporation, "Long-term dietary toxicity/carcinogenicity study in rats," 410-011, August 27, 1982.
4. Ibid., p. 27.
5. International Research and Development Corporation, "Long-term dietary toxicity/carcinogenicity study in mice," 410-005, August 27, 1982.
6. Primate Research Institute, New Mexico State University, "An endocrine evaluation of the thyroidal effects of FD&C Red #3," Study No. CM-70r, October 17, 1983, p. 27.
7. Tox. Eval. of Some Food Additives, No. 55A, FAO Nutrition Meeting Report Series, 1975. Studies cited are: Z. Lebensmitt Untersuch 122, 157, 1960; Path. et Microbiol. 26, 206, 1963.
8. Ishidate, M., et al., Primary mutagenicity screening of food additives currently used in Japan. Ed. Chem. Toxic. 22:623-6.
9. Collins, T.F.X., Long, E.L., Effects of chronic oral administration of erythrosine in the Mongolian gerbil. Food Cosmet. Toxicol., 14:223.
10. 48 Fed. Reg. 45237 (October 4, 1983).
11. Ibid.
12. Minutes of NTP Peer Review Panel Meeting, Research Triangle Park, North Carolina, October 27, 1983, p. 5.
13. Food Chemical News, June 4, 1984.
14. Letter from Senators Tower, Symms, Hatfield, Packwood, Helms, McClure, Garn and D'Amato to Margaret M. Heckler, Secretary, Department of Health and Human Services, May 21, 1984.

Dye: FD&C Yellow No. 5 (Tartrazine)

Major Uses: Predominantly food (pet food, bakery goods, beverages).¹

Pounds certified by FDA:²

1982: 1,456,048

1983: 1,470,615

1984: 1,620,540

Current Status: Provisionally listed for use in cosmetics and externally applied drugs; salt permanently listed for use in food and ingested drugs; lake provisionally listed for use in food and ingested drugs.

No. of extensions of provisional listing since February, 1981: 9

Summary of evidence against permanent listing:

It is now 2-3 years since the chronic feeding studies on FD&C Yellow No. 5 were completed. The conclusions of those studies and others are summarized below:

--1981 long-term mouse feeding study³ (doses: 0.5%, 1.5%, 5.0%) showed:

- a. statistically significant increase in lymphocytic lymphoma in low dose females.
- b. increase in lymphocytic lymphoma in mid dose males.

--1981 long-term rat feeding study⁴ (doses: 0.1%, 1.0%, 2.0%) showed:

- a. statistically significant increase in thyroid follicular adenomas in high dose females.
- b. statistically significant trend test for the incidence of endometrial polyps.

--1982 long-term rat feeding study⁵ (dose: 5.0%) found:

- a. statistically significant reduction in weight gain for both males and females.
- b. increases in thyroid C-cell adenomas in males and lymphocytic lymphoma in females.

--Earlier studies have shown an increase in lung tumors in mice⁶ and an increase in mammary fibroadenomas in rats.⁷

--Evidence of FD&C Yellow No. 5-induced chromosomal aberrations.^{8,9}

--The ability of FD&C Yellow No. 5 to induce allergic reactions is well known¹⁰⁻¹². One study has found that 70% of people who are allergic to aspirin will be allergic to FD&C Yellow No. 5.¹³

An FDA Internal Analgesic Report stated that 0.2% of the general U.S. population is allergic to aspirin.¹⁴ Thus, upwards of 300,000 people in the U.S. are allergic to FD&C Yellow No. 5, a figure that is surely an understatement since some patients who are not allergic to aspirin will be allergic to FD&C Yellow No. 5.¹⁵ Despite the current labeling standard, common circumstances (restaurants, parties, dinner with friends) in which the allergic person does not see the label argue strongly against the continued use of FD&C Yellow No. 5.

--FDA has noted that FD&C Yellow No. 5 contains known carcinogens.¹⁶

--FD&C Yellow No. 5 has been banned in Norway.¹⁷

Footnotes for FD&C Yellow No. 5

1. National Academy of Sciences, "Food Colors," Washington, D.C., 1971.
2. Division of Color Technology, Certification Branch.
3. International Research and Development Corporation, "Long-term dietary toxicity/carcinogenicity study in mice," 410-006, August 31, 1981.
4. International Research and Development Corporation, "Long-term dietary toxicity/carcinogenicity study in rats," 410-003, August 31, 1981.
5. International Research and Development Corporation, "Long-term dietary toxicity/carcinogenicity study in rats," 410-012, August 27, 1982.
6. Acta. Physiol. Neerlandica 7, 35-55, 1958.
7. Davis, K.J., Fitzbaugh, O.G., Nelson, A.A., Chronic rat and dog toxicity studies on tartrazine. Toxicology and Applied Pharmacology 6, pp. 621-6, 1964.
8. Patterson, R.M. Butler, J.S., Tartrazine-induced chromosomal aberrations in mammalian cells. Ed. Chem. Toxic. 20:461-465.
9. Ishidate, M., et al. Primary mutagenicity screening of food additives currently used in Japan. Ed. Chem. Toxic. 22:623-636.
10. Annals of Allergy 17, 719, 1959.
11. Michaelsson, G., Juhlin, L., Urticaria induced by preservatives and dye additives in food and drugs. British Journal of Dermatology (1973) 88, 525.
12. Miller, K., Sensitivity to Tartrazine. British Medical Journal, Vol. 285, 4 December, 1982, p. 1597.
13. Michaelsson, G., op. cit.
14. Food and Drug Administration, Internal Analgesic Report (Draft No. 6), October 1976, p. 327.
15. Michaelsson, G., op cit.
16. Food Chemical News, February 13, 1984.
17. International Life Sciences Institute, Catalog of Food Colors, June 4, 1984.

Dye: FD&C Yellow No. 6 (Sunset Yellow FCF)

Major Uses: Predominantly food (beverages, sausage, candy, dessert powders)¹

Pounds certified by FDA:²

1982: 1,154,590

1983: 1,086,581

1984: 1,535,050

Current Status: Provisionally listed for use in food, drugs, and cosmetics.

No. of extensions of provisional listing since February, 1981: 7

Summary of evidence against permanent listing:

FDA has had in its possession studies indicating the lack of safety of FD&C Yellow No. 6 for 2 years.

--1982 long-term feeding study³ in rats (doses: 0.175%, 1.5%, 3.0%) found:

a. statistically significant increase in adrenal medullary adenomas in high dose females.

b. statistically significant increase in testicular interstitial adenomas in high dose males.

c. increase in the following in the high dose group: cardiovascular hemangiomas in males, adrenal cortical and pancreatic islet cell adenomas, squamous cell carcinomas of the skin and total malignant tumors in females.

--1982 long-term feeding study⁴ in rats (dose: 5.0%) found:

a. increased incidences of renal cortical adenomas/carcinomas in males and females.

b. hyperplasia of the testis and female adrenal medulla.

c. increase in mortality and decrease in body weight in males and females.

d. increase in splenic nodules and hemangiosarcomas of the spleen in males.

In an interim report on the renal neoplasms in the high dose female rats, Dr. Robert Squire, a consultant to the Certified Color Manufacturers Association, concluded that those neoplasms represented "preliminary evidence of a compound-related renal carcinogenic effect."⁵

--Adverse drug reactions associated with FD&C Yellow No. 6.⁶

--Evidence of mutagenicity for FD&C Yellow No. 6.⁷

--FD&C Yellow No. 6 has been found to induce chromosomal damage in Chinese hamster fibroblast cell lines.⁸

--FDA has noted that FD&C Yellow No. 6 contains known carcinogens.⁹

--FD&C Yellow No. 6 has been banned in Norway and Sweden.¹⁰

Footnotes for FD&C Yellow No. 6

1. National Academy of Sciences, "Food Colors," Washington, D.C., 1971.
2. Division of Color Technology, Certification Branch.
3. Bio/dynamics, "A long-term toxicity/carcinogenicity study of FD&C Yellow #6 in rats," Project No. 77-1778, December 31, 1982.
4. Bio/dynamics, "A long-term oral toxicity/carcinogenicity study of 5.0% FD&C Yellow No. 6 in rats," Project No. 78-2211, December 31, 1982.
5. Letter from Richard A. Squire, D.V.M, Ph.D., to Herbert Ray, Certified Color Manufacturers Association, August 17, 1984.
6. Jenkins, P., Michelson, R., Emerson, P.A., "Adverse drug reaction to sunset-yellow in rifampicin/isoniazid tablet," Lancet, August 14, 1982, p. 385.
7. Sysoev, A.B., Zhurkov, V.S., A study of the mutagenic activity of synthetic food dyes - sun yellow sunset FCF and its analogous compound - sun yellow K. Gig. i Sanit. 1974, 9, pp. 26-30.
8. Ishidate, M., et al, Primary mutagenicity screening of food additives currently used in Japan. Ed. Chem. Toxic. 22:623-636.
9. Food Chemical News, February 13, 1984.
10. International Life Sciences Institute, Catalog of Food Colors, June 4, 1984.

Dyes: D&C Reds Nos. 8&9

Major Uses: Drugs and cosmetics (primarily lipstick)¹

Pounds certified by FDA:²

<u>D&C Red No. 8</u>	<u>Salt</u>	<u>Lake</u>
1982:	483	1,864
1983:	976	0
1984:	0	0

<u>D&C Red No. 9</u>	<u>Salt</u>	<u>Lake</u>
1982:	0	66,243
1983:	0	35,334
1984:	0	24,571

Current Status: Provisionally listed for use in internally and externally applied drugs and cosmetics.

No. of extensions of provisional listing since February, 1981: 9

Summary of evidence against permanent listing:

3 years have elapsed since the completion of long-term feeding studies indicating the carcinogenicity of D&C Reds Nos. 8&9. The most significant carcinogenic/toxic effects of D&C Red No. 9 are manifested in the spleen or are related to that splenic toxicity.

--1982 long-term rat feeding study³ (dose: 1.0%) found:

a. highly unusual mesenchymal neoplasms of the spleen associated with the administration of D&C Red No. 9 in males and females.

b. compound-related decreases in red blood cell parameters (red blood cell count, packed red cell volume and hemoglobin percent) and an increased reticulocyte count in males and females.

c. significant increases in spleen weight, splenic extra-medullary hematopoiesis, splenic congestion, splenic fibrosis, splenic mesothelial hyperplasia, splenic mesothelial cyst formation, splenic capsular fibrosis and multifocal cellular proliferations in the splenic capsule.

d. compound-related hemosiderin deposition in a variety of organs.

--1981 NTP bioassay⁴ in rats (doses: 0.1%, 0.3%) and mice (doses: 0.1%, 0.2%) found:

a. statistically significant increase in fibrosarcomas of the spleen in high dose male rats.

b. statistically significant increase in total sarcomas of the spleen, splenic capsule or splenic pulp of high dose male rats.

c. other splenic lesions appeared at increased incidences in male and female rats: splenic congestion, focal or multifocal fibrosis, pigment deposition, diffuse fibrosis and fatty metamorphosis.

The NTP thus concluded 3 years ago: "The association between administration of D&C Red No. 9 in the diet and splenic neoplasia in male rats and splenic toxicity in rats of both sexes, therefore, is unequivocal."⁵ FDA agrees with the NTP that "the splenic tumors seen in the study were compound related"⁶ and Dr. Sanford A. Miller, Director of FDA's Center for Food Safety and Applied Nutrition, has noted that both D&C Reds Nos. 8&9 will be absorbed through the skin at "significant levels."⁷ Further grounds for concern over the safety of D&C Red No. 9 came from a study of the splenic lesions noted in the NTP bioassay which found that the treatment-related, nonneoplastic splenic lesions (hemorrhage, fibrosis, fatty metamorphosis and capsular hyperplasia) were preneoplastic.⁸ Other reputable scientific bodies concur with the finding of carcinogenicity. FDA's Cancer Assessment Committee concluded that D&C Red No. 9 "is carcinogenic to male Fischer 344 rats, inducing various types of sarcoma of the spleen,"⁹ while the Federation of American Societies for Experimental Biology (FASEB) found "limited" evidence of carcinogenicity in its review of D&C Red No. 9.¹⁰

The NTP bioassay¹¹ also gave evidence of hepatic carcinogenicity:

d. statistically significant increase in hepatic neoplastic nodules in male and female rats.

e. statistically significant increase in hepatocellular carcinomas in male mice.

Footnotes for D&C Reds Nos. 8&9

1. Life Sciences Research Office, Federation of American Societies for Experimental Biology, "Interim Scientific Report on Evaluation of the Evidence of Carcinogenicity and Genotoxicity of Drugs and Cosmetic Ingredients," March, 1984.

2. Division of Color Technology, Certification Branch.

3. Litton Bionetics, Inc., "30-month chronic toxicity and potential carcinogenicity study in rats with in utero and lifetime exposure to D&C Red No. 9 in the diet," LBI Project No. 20957, July 1982.

4. National Cancer Institute, NTP Carcinogenesis Technical Report Series No. 225, "Carcinogenesis bioassay of D&C Red No. 9 in F344 rats and B6C3F1 mice (feed study)," Dept. of HHS Publication No. 82-1781, Washington, D.C., 1981.

5. Ibid., p. 60.

6. Memorandum of conference between FDA and CTFA, November 23, 1982. 23, 1982.

7. Food Chemical News, November 15, 1982.

8. Weinberger, M.A., Albert, R.H., Montgomery, S.B., "Preneoplastic splenic lesions in F344 rats fed high doses of D&C Red No. 9 or aniline hydrochloride."

9. Lorentzen, R.J. Memorandum of conference of FDA Cancer Assessment Committee, July 7, 1981, June 24 and August 26, 1982.

10. Life Sciences Research Office, op. cit.

11. National Cancer Institute, op. cit.

Dye: D&C Red No. 33 (Acid Fuschine D)

Major Uses: Drugs and cosmetics

Pounds certified by FDA:¹

	Salt	Lake
1982:	6,665	3,655
1983:	7,447	830
1984:	18,811	1,130

Current Status: Provisionally listed for use in internally and externally applied drugs and cosmetics.

No. of extensions of provisional listing since February, 1981: 12

Summary of evidence against permanent listing:

Over 2 years have elapsed since the completion of long-term feeding studies on D&C Red No. 33. The dye exhibited toxic effects in the spleen and kidney and caused "dose-related"² anemia. The following effects were observed in the spleen:

--1982 long-term rat feeding study³ (dose: 2.0%) found:

- a. splenomegaly in both sexes throughout the study.
- b. one fibrosarcoma and one fibroma in the spleens of male rats.
- c. a variety of nonneoplastic splenic lesions: diffuse congestion, pigment deposition and proliferative fibroblastic lesions.

--Pigment deposition in the spleen was found in a 1982 long-term mouse feeding study⁴ (doses: 0.1%, 1.0%, 5.0%) which had to terminate prematurely due to "compound-related reduced survival"⁵ in both sexes.

The nonneoplastic splenic lesions observed in the spleens in the rat study above are similar to those observed with the chronic administration of D&C Red No. 9, for which a review⁶ has concluded that the lesions are preneoplastic. FDA's Cancer Assessment Committee thus notes that "in light of present knowledge ... there is considerable concern that the color additive has the potential to be a carcinogen."⁷

Toxic lesions in the kidney included the following:

--1982 long-term rat feeding study⁸ (dose: 2.0%) found:

- a. increases in kidney size and "compound-related"⁹ chronic progressive nephropathy in both sexes.
- b. pigment deposition in the kidneys of males and females.

--1982 long-term mouse feeding study¹⁰ (doses: 0.1%, 1.0%, 5.0%) exhibited "chronic renal disease"¹¹ characterized by chronic nephritis, hydronephrosis and tubular pigment deposition in high dose mice of both sexes.

The evidence of anemia was as follows:

--Depressed red cell parameters and elevated reticulocyte counts in 2 studies^{12, 13} in both sexes.

--Statistically significant increases in reticulocyte counts in mid dose females and high dose males and females in the first half of a third study.¹⁴

Upon the request of FDA, the D&C Red No. 33 test data were reviewed by an NTP Peer Review Panel, which concluded that the rates of splenic changes in the high dose rat study¹⁵ "could not be considered sufficient to be categorized as a demonstrated carcinogenic response." Declaring that "further research is necessary," the NTP noted that "[q]ualitatively, there appears to be treatment-related nonneoplastic target organ (spleen) toxic responses similar to those previously described for certain other aromatic azo compounds, aromatic nitro compounds, and amines."¹⁶

Footnotes for D&C Red No. 33

1. Division of Color Technology, Certification Branch.
2. International Research and Development Corporation, "Long-term feeding study in mice," 355-007, March 26, 1982, p. 16.
3. International Research and Development Corporation, "Long-term feeding study in rats exposed in utero," 355-017, March 26, 1982.
4. See note 2.
5. Ibid., p. 2.
6. Weinberger, M.A., Albert, R.H., Montgomery, S.B., "Preneoplastic splenic lesions in F344 rats fed high doses of D&C Red No. 9 or aniline hydrochloride."
7. Memorandum of meeting of Cancer Assessment Committee, November 10, 1983.
8. See note 3.
9. Ibid., p. 31.
10. See note 2.
11. Ibid., p. 20.
12. See note 2.
13. See note 3.
14. International Research and Development Corporation, "Long-term feeding study in rats exposed in utero," 355-009, March 26, 1982.
15. See note 3.
16. Minutes of NTP Board of Scientific Counselors' Meeting, Research Triangle Park, North Carolina, July 26, 1984, p. 5.

Dye: D&C Orange No. 17

Major Uses: Drugs and cosmetics

Pounds certified by FDA:¹

	Salt	Lake
1982:	7,026	18,381
1983:	2,191	6,114
1984:	0	1,083

Current Status: Provisionally listed for use in externally applied drugs and cosmetics.

No. of extensions of provisional listing since February, 1981: 11

Summary of evidence against permanent listing:

Chronic feeding studies completed over 2 years ago have shown the following lesions in the liver:

--1982 long-term rat feeding study² (dose: 1.0%) found:

- a. statistically significant increase in hepatocellular adenomas in females.
- b. statistically significant increase in total hepatocellular neoplasms in females.
- c. increase in hepatocellular carcinomas in males.
- d. a variety of nonneoplastic findings in the liver in both sexes.

--1982 long-term mouse feeding study³ (doses: 0.025%, 0.25%, 1.0%) found an increase in total hepatocellular neoplasms in high dose males.

Bio/dynamics has stated "the pattern is that the compound is associated with a shorter lifespan in the [male mice]. The compound is also associated with an earlier tumor onset, specifically tumors of the liver, in the males."⁴

Other pertinent findings included:

--Statistically significant increase in the number of high dose female rats with tumors of the lymphoreticular system, all sites.⁵

--Increase in fibroadenomas of the mammary gland in female rats.⁶

--Compound-related pigment deposition in the brain, spinal cord, thyroid, heart, stomach, spleen, cecum and liver in high dose mice.⁷

--D&C Orange No. 17 has been found to be mutagenic in an Ames short-term test.⁸

On April 1, 1983, FDA terminated the provisional listing of D&C Orange No. 17 for ingested uses.⁹ FDA stated subsequently: "The agency has concluded that D&C Orange No. 17 is an animal carcinogen when administered in the diet, based on the increased incidence of hepatocellular neoplasms in two mammalian species."¹⁰

Footnotes for D&C Orange No. 17

1. Division of Color Technology, Certification Branch.
2. Bio/dynamics, "A long-term toxicity/carcinogenicity study of 1.0% D&C Orange #17 in rats," Project No. 78-2244, March 29, 1982.
3. Bio/dynamics, "A long-term feeding study with D&C Orange #17 in mice," Project No. 77-1883, March 29, 1982.
4. F-D-C Reports, August 30, 1982.
5. Bio/dynamics, "A long-term oral toxicity/carcinogenicity study of D&C Orange #17 in rats," Project No. 77-1882, March 29, 1982.
6. See note 2.
7. See note 3.
8. Brown, J.P., Dietrich, P.S., Bakner, C.M. Mutagenicity testing of some drug and cosmetic dye lakes with the Salmonella/-mammalian microsome assay. Mutat. Res. 66:181-185.
9. 48 Fed. Reg. 13976 (April 1, 1983).
10. 48 Fed. Reg. 44774 (September 30, 1983).

Dyes: D&C Reds Nos. 19 (Rhodamine B) & 37

Major Uses: Drugs and cosmetics (lipstick, cologne, nail polish enamel, perfumes, shampoos, creams and hair preparations)¹

Pounds certified by FDA:²

<u>D&C Red No. 19</u>	<u>Salt</u>	<u>Lake</u>
1982:	1,633	14,396
1983:	441	3,395
1984:	1,365	5,600

D&C Red No. 37

1982:	0	0
1983:	0	0
1984:	0	0

Current Status: Provisionally listed for use in externally applied drugs and cosmetics.

No. of extensions of provisional listing since February, 1981: 13

Summary of evidence against permanent listing:

Chronic feeding studies confirming the carcinogenicity of D&C Reds Nos. 19&37 have been completed for almost 3 years.

--1981 long-term rat feeding study³ (doses: 0.002%, 0.005%, 0.02%) found an increase in astrocytomas of the brain and/or spinal cord and granular cell tumors of the brain in high dose males; a similar incidence of granular cell tumors was found in the mid dose males.

--1981 long-term rat feeding study⁴ (dose: 0.075%) found an increased incidence of thyroid follicular cell adenomas and carcinomas and parathyroid adenomas in the treated males.

--1981 long-term mouse feeding study⁵ (doses: 0.005%, 0.02%, 0.10%) found an increased incidence of hepatocellular carcinomas in the mid- and high dose females; hepatocytomegaly was increased in high dose males.

--D&C Red No. 19 has been shown to be mutagenic in Salmonella/-microsome assays.^{6,7}

--D&C Red No. 19 has caused an increase in chromosomal aberration and sister-chromatid exchange in Chinese hamster ovary cells.⁸

--D&C Red No. 19 was also positive in a Bacillus subtilis rec assay as well as for chromosomal aberrations in hamster lung fibroblast cells.⁹

On February 4, 1983¹⁰, FDA terminated the provisional listing of D&C Reds Nos. 19&37 for ingested uses because "... these color additives have been shown to be animal carcinogens upon ingestion."¹¹ Dr. Sanford A. Miller, Director of FDA's Center for Food Safety and Applied Nutrition, noted as early as 1982 FDA's intent to cease the provisional listing of D&C Reds Nos. 19&37 for all uses. Said Miller: "The two latest feeding studies conducted for CTFA indicate that D&C Red No. 19 induces carcinogenic effects when fed to rats and mice. Moreover, because in [CTFA's] latest submission you report that D&C Red Nos. 19&37 are expected to be absorbed percutaneously ... we believe the provisions of the Color Additive Amendments would require prohibition of the use of these color additives in externally applied drugs and

cosmetics."¹² Over 2 years have elapsed since that declaration without FDA action.

The carcinogenicity of D&C Red No. 19 has continued to be reviewed. Most recently a FASEB panel concluded that "there is adequate evidence of carcinogenicity of certified preparations of D&C Red No. 19 in two rodent species."¹³ The Canadian government has acted more expeditiously to protect its populace; D&C Red No. 19 was banned for external use there almost 3 years ago.¹⁴

Footnotes for D&C Reds Nos. 19 & 37

1. Life Sciences Research Office, Federation of American Societies for Experimental Biology, "Interim Scientific Report on Evaluation of the Evidence of Carcinogenicity and Genotoxicity of Drugs and Cosmetic Ingredients," March, 1984.
2. Division of Color Technology, Certification Branch.
3. Bio/dynamics, "A long-term oral toxicity/carcinogenicity study of D&C Red #19 in rats," Project No. 77-1880, December 30, 1981.
4. Bio/dynamics, "A long-term oral toxicity/carcinogenicity study of 0.075% D&C Red #19 in rats," Project No. 78-2243, December 30, 1981.
5. Bio/dynamics, "A long-term feeding study of D&C Red #19 in mice," Project No. 77-1881, December 30, 1981.
6. Nestmann, E.R., Douglas, G.R., Matula, T.I., Grant, C.E., Dowbel, D.J. 1979. Mutagenic activity of rhodamine dyes and their impurities as detected by mutation induction in Salmonella and DNA damage in Chinese hamster ovary cells. Cancer Res. 39:4412-4417.
7. Brown, J.P., Dietrich, P.S., Bakner, C.M. 1979. Mutagenicity testing of some drug and cosmetic dye lakes with Salmonella/mammalian microsome assay. Mutat. Res. 66:181-185.
8. Au, W., Hsu, T.C. 1979. Studies on the clastogenic effects of biologic stains and dyes. Environ. Mutagen. 1:27-35.
9. Kawachi, T., et al 1980. Cooperative programme on short-term assays for carcinogenicity in Japan. IARC Sci. Pub. 27:323-330.
10. 48 Fed. Reg. 5262 (February 4, 1983).
11. 48 Fed. Reg. 8444 (March 1, 1983).
12. Food Chemical News, November 15, 1982.
13. Life Sciences Research Office, op. cit.
14. Food Chemical News, January 25, 1982.

Dye: D&C Red No. 36

Major Uses: Drugs and cosmetics

Pounds certified by FDA:¹

	Salt	Lake
1982:	3,544	0
1983:	3,641	0
1984:	6,413	0

Current Status: Provisionally listed for use in externally applied drugs and cosmetics.

No. of extensions of provisional listing since February, 1981: 3

Summary of evidence against permanent listing:

Over one year has elapsed since the conclusion of long-term studies on D&C Red No. 36.

--1983 long-term rat feeding study² (dose: 2.0%) found:

a. statistically significant increase in fibroadenomas and combined adenomas and fibroadenomas of the mammary gland in females.

b. statistically significant increase in the number of animals with benign tumors.

c. a variety of nonneoplastic splenic lesions in both sexes: hemosiderosis, congestion, fibrosis, mesothelial hyperplasia and extramedullary hematopoiesis.

d. depressed red cell parameters and elevated reticulocyte counts in both sexes.

e. increase in stomach lesions (predominantly forestomach ulcers) in males.

f. depressions in body weight in treated groups.

Of particular note in this study is the fact that, although the number of females at scheduled death with adenomas/fibroadenomas did not differ between control and treated groups, animals dying unscheduled deaths were more likely to have adenomas/fibroadenomas. For fibroadenomas and combined adenomas and fibroadenomas this increase was statistically significant, suggesting that the mammary tumors were the cause of the statistically significant increase in unscheduled deaths seen in the treated group.

--1983 long-term rat feeding study³ (doses: 0.01%, 0.025%, 0.10%) found a statistically significant increase in combined adenomas and fibroadenomas of the mammary gland in high dose females.

--1983 long-term mouse feeding study⁴ (doses 0.05%, 1.0%, 5.0%) found:

a. statistically significant increase in the number of high dose males with myelomonocytic leukemia.

b. significant increase in mortality in mid- and high dose males.

--D&C Red No. 36 has been shown to be mutagenic in Salmonella/-microsome assays.⁵

Footnotes for D&C Red No. 36

1. Division of Color Technology, Certification Branch.
2. Litton Bionetics, Inc., "30-month chronic toxicity and potential carcinogenicity study in rats with in utero and lifetime exposure to D&C Red No. 36 in the diet," LBI Project No. 21164, September, 1983.
3. Litton Bionetics, Inc., "30-month chronic toxicity and potential carcinogenicity study in rats with in utero and lifetime exposure to D&C Red No. 36 in the diet," LBI Project No. 20833, September, 1983.
4. Litton Bionetics, Inc., "Chronic toxicity and potential carcinogenicity study in the mouse: D&C Red No. 36," LBI Project No. 20835, September, 1983.
5. Brown, J.P., Dietrich, P.S., Bakner, C.M. 1979. Mutagenicity testing of some drug and cosmetic dye lakes with Salmonella/mammalian microsome assay. Mutat. Res. 66:181-185.