

7. It will establish safeguards to prohibit employees from using their positions for a purpose that is or gives the appearance of being motivated by a desire for private gain for themselves or others, particularly those with whom they have family, business, or other ties.

8. It will give the sponsoring agency or the Comptroller General through any authorized representative the access to and the right to examine all records, books, papers, or documents related to the grant, including the records of contractors and subcontractors performing under the grant.

9. It will comply with requirements imposed by the Federal sponsoring agency concerning special requirements of law, program requirements, and other administrative requirements.

10. It will insure that the facilities under its ownership, lease or supervision which shall be utilized in the accomplishment of the project are not listed on the Environmental Protection Agency's (EPA) list of Violating Facilities and that it will notify the Federal grantor agency of the receipt of any communication from the Director of the EPA Office of Federal Activities indicating that a facility to be used in the project is under consideration for listing by the EPA.

The phrase "Federal financial assistance" includes any form of loan, grant, guaranty, insurance payment, rebate, subsidy, disaster assistance loan or grant, or any other form of direct or indirect Federal assistance.

11. It will comply with the flood insurance purchase requirements of Section 102(a) of the Flood Disaster Protection Act of 1973, Public Law 93-234, 87 Stat. 975, approved December 31, 1976. Section 102(a) requires, on and after March 2, 1975, the purchase of flood insurance in communities where such insurance is available as a condition for the receipt of any Federal financial assistance for construction or acquisition purposes for use in any area that has been identified by the Secretary of the Department of Housing and Urban Development as an area having special flood hazards.

12. It will assist the Federal grantor agency in its compliance with Section 106 of the National Historic Preservation Act of 1966 as amended (16 U.S.C. 470), Executive Order 11593, and the Archeological and Historic Preservation Act of 1966 (16 U.S.C. 469a-1 et seq.) by (a) consulting with the State Historic Preservation Officer on the conduct of investigations, as necessary, to identify properties listed in or eligible for inclusion in the National Register of Historic Places that are subject to adverse effects (see 36 CFR Part 800.8)

by the grantee's activity and notifying the Federal grantor agency of the existence of any such properties, and by (b) complying with all requirements established by the Federal grantor agency to avoid or mitigate adverse effects upon such properties.

13. Applicants for the Administration for Native Americans Programs, hereby certify in accordance with 45 CFR 1336.53, that the financial assistance provided by the Office of Human Development Services for the specified activities to be performed under this program, will be in addition to, and not in substitution for, comparable activities provided without Federal assistance.

14. It will comply with the Age Discrimination Act of 1975 enacted as an amendment to the Older Americans Act (Pub. L. 94-135), which provides that: No person in the United States shall, on the basis of age be excluded from participation in, be denied the benefits of, or be subjected to discrimination under, any program or activity for which the applicant receives Federal financial assistance.

15. It will comply with Section 504 of the Rehabilitation Act of 1973, as amended (29 U.S.C. 794), all requirements imposed by the applicable HHS regulation (45 C.F.R. Part 84), and all guidelines and interpretations issued pursuant thereto, which prohibits discrimination on the basis of handicap in programs and activities receiving Federal financial assistance.

16. It will comply with Title IX of the Education Amendments of 1972 (20 U.S.C. 1681, et seq.) which prohibits discrimination on the basis of sex in education programs and activities receiving Federal financial assistance (whether or not the programs or activities are offered or sponsored by an educational institution).

17. It will comply with Pub. L. 93-348 as implemented by Part 46 of Title 45 (45 CFR 46, 42 U.S.C. 2891) regarding the protection of human subjects involved in research, development, and related activities supported by the grant.

18. It will comply with the equal opportunity clause prescribed by Executive Order 11246, as amended, and will require that its subrecipients include the clause in all construction contracts and subcontracts which have or are expected to have an aggregate value within a 12-month period exceeding \$10,000, in accordance with Department of labor regulations at 41 CFR Part 60.

19. It will include, and will require that its subrecipients include, the provision set forth in 29 CFR 5.5(c) pertaining to overtime and unpaid wages in any nonexempt

nonconstruction contract which involves the employment of mechanics and laborers (including watchmen, guards, apprentices, and trainees) if the contract exceeds \$2,500.

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BILLING CODE 4150-04-M

## Food and Drug Administration

[Docket No. 83C-0129]

### Color Additives; Denial of Petition for Listing of D&C Red No. 19 for Use in Externally Applied Drugs and Cosmetics

**AGENCY:** Food and Drug Administration.  
**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is denying the color additive petition to permanently list D&C Red No. 19 for use in externally applied drugs and cosmetics. This action is based upon previous findings of FDA that this color additive is carcinogenic in test animals and the finding of the U.S. Court of Appeals for the District of Columbia that D&C Red No. 19, which had been found to be a carcinogen in animals, cannot be listed as a color additive in externally applied drugs and cosmetics on the basis of a *de minimis* exception to section 706(b) of the Federal Food, Drug, and Cosmetic Act (the act). In a final rule published elsewhere in the issue of the *Federal Register*, FDA is removing the regulations permanently listing D&C Red No. 19 for use in externally applied drugs and cosmetics and removing the regulation that provides for the provisional use of its lakes.

**DATE:** Objections by August 15, 1988.

**ADDRESS:** Written objections may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Gerard L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

#### SUPPLEMENTARY INFORMATION:

##### I. Introduction

D&C Red No. 19, which has been in use for many years, is principally the 3-ethochloride of 9-*o*-carboxyphenyl-6-diethylamino-3-ethylamino-3-isoxanthene (CAS Reg. No. 81-88-9). Because D&C Red No. 19 was in use at the time the Color Additive Amendments of 1960 were enacted, it

was provisionally listed for drug and cosmetic use in the **Federal Register** of October 12, 1960 (25 FR 9759)

## II. Regulatory History

D&C Red No. 19 is the subject of a color additive petition (CAP 9C0091) that was submitted by the Toilet Goods Association, Inc. (CTFA), 1100 Vermont Ave. NW., Washington, DC 20005) on April 14, 1969, which requested the permanent listing of D&C Red No. 19 for coloring lipsticks, ingested drugs and cosmetics, and externally applied drugs and cosmetics.

In the **Federal Register** of February 4, 1977 (44 FR 6992), FDA published revised provisional regulations which required new chronic toxicity studies on 31 color additives, including D&C Red No. 19, as a condition for continued provisional listing of these color additives.

In the **Federal Register** of February 4, 1983 (48 FR 5262) FDA published a final rule terminating the provisional listing of D&C Red No. 19 for use in ingested drugs and cosmetics. This document acknowledged the withdrawal by CTFA of that portion of CAP 9C0091 that requested permanent listing of D&C Red No. 19 for ingested drugs and cosmetics. The color additive remained provisionally listed for use in externally applied drugs and cosmetics. In the February 4, 1983, document terminating the provisional listing of D&C Red No. 19 FDA explained the findings that D&C Red No. 19 was a carcinogen when ingested by test animals. The rationale for this decision is stated in detail in the **Federal Register** of February 4, 1983. CTFA did not object to the finding of carcinogenicity.

In the **Federal Register** of August 7, 1986 (51 FR 28346), FDA published a final regulation permanently listing D&C Red No. 19 for use in externally applied drugs and cosmetics. In the August 7, 1986, document FDA concluded that the results of chronic toxicity studies demonstrate that D&C Red No. 19 is carcinogenic when administered in the diet to laboratory mice and rats. Specifically, the agency concluded from the data that dietary exposure to D&C Red No. 19 causes an increase in the number of female mice with hepatocellular neoplasms. Likewise, the agency determined that D&C Red No. 19 in the diet induces neoplasms in the thyroid gland of male rats and a tumorigenic effect in the parathyroid of male rats.

In its submissions in support of its petition, CTFA presented several arguments that raised questions about the relevance of the ingestion studies to a determination of the safety of the

external uses of D&C Red No. 19. The entire discussion of FDA's determination that this color additive induced cancer in animals, including FDA's responses to the issues raised by CTFA, as summarized below, appeared in the listing document in the **Federal Register** (51 FR 28346).

### A. Difference in Reported Incidence Figures

In the submissions, CTFA noted that the tumor incidence data on the mouse study and a rat study as reported by FDA (48 FR 5262) in its order terminating the provisional listing of D&C Red No. 19 for use in ingested cosmetics and drugs differed from those reported by the testing laboratory. FDA explained in the August 7, 1986, document that the difference was due largely to a different interpretation of the data by FDA pathologists compared to the interpretation of the data by the pathologists from the testing laboratory. The conclusions, however were the same, namely that dietary exposure to D&C Red No. 19 causes treatment or dose-related increases of tumors in mice and rats.

### B. Interpretation of Maximum Tolerated Dose

In the submissions CTFA asserted that the maximum tolerated dose was exceeded in the second of the rat studies with D&C Red No. 19 and this violated the National Cancer Institute (NCI) guidelines for carcinogenicity testing, thereby raising questions about the carcinogenic effect observed with the dose (0.075 percent) in this study. FDA concluded that there was no indication whatsoever that the maximum tolerated dose was exceeded in the male rats tested (the gender shown to be positive in the study—thus CTFA's arguments on this issue were of little relevance and impact.

### C. Significance of Mouse Liver Tumors

In its submissions, CTFA questioned the significance of the mouse liver tumors observed in the chronic tests. FDA evaluated the arguments presented by CTFA and concluded that, based on the agency's analysis of the data, the hepatocellular tumors observed in the female mice were the result of the ingestion of D&C Red No. 19 and must be considered in any evaluation of the safety of the color additive.

### D. Mechanism of Carcinogenicity

CTFA stated in its submissions that it reviewed the information available on D&C Red No. 19 to determine the likely mechanism of action of the additive and contended that currently available

evidence does not demonstrate that D&C Red No. 19 is a primary carcinogen. CTFA presented arguments based upon the results of mutagenicity studies to support its contention. FDA concluded that the arguments CTFA presented regarding mutagenicity (and impurity activity) do not provide evidence that D&C Red No. 19 is not a carcinogen.

CTFA also argued that it is possible that a secondary mechanism may have caused each of the types of tumors observed in the chronic bioassays of D&C Red No. 19.

In response to the several arguments presented by CTFA, FDA stated that the arguments were speculative, and CTFA had not submitted factual evidence that D&C Red No. 19 does indeed act as a secondary carcinogen. Finally, FDA concluded that CTFA had failed to present any basis on which to find that D&C Red No. 19 is a secondary carcinogen.

In the document permanently listing this color FDA concluded that although studies established that the color additive caused cancer in animals, quantitative risk assessment of the color indicated that the risk of human cancer from its use in externally applied drugs and cosmetics would be extremely low, and that there would be no benefit to the public from prohibiting these uses of the color additive. Thus, FDA concluded that the uses of D&C Red No. 19 in externally applied drugs and cosmetics was safe under the conditions of use prescribed in the regulations permanently listing the color additive.

FDA also concluded that it was appropriate for the agency to apply a *de minimis* exception to the Delaney clause of the act where the color additives impose essentially no additional risk of cancer to the public; that any risk the color additives may present is of no public health consequence; and that, under these circumstances, the Delaney clause does not require a ban of the externally applied use of D&C Red No. 19.

In response to the permanent listing of D&C Red No. 19, the Public Citizen Litigation Group (Public Citizen) filed objections on August 21, 1986, which stayed the effective date of the regulation. Public Citizen, however, did not request a hearing. Additionally, on September 8, 1986, CTFA filed comments in support of FDA's permanent listing of D&C Red No. 19.

The CTFA comments specifically stated that CTFA supported the permanent listing of the color additive. The comments did not represent objections to the listing rule. In the introduction to its comments, however,

CTFA asserted that some cancer experts consider the liver of the inbred mouse to be an invalid system for carcinogenicity testing and the comments stated that these experts considered mouse liver tumors to be of limited relevance to human risk because of the extreme sensitivity of the mouse liver to chemical insult. FDA finds that CTFA's arguments on this subject were discussed in detail in the **Federal Register** in the listing document (51 FR 28346 at 28351). CTFA did not present any new data in support of its position and did not request a hearing on the subject.

CTFA also postulated that thyroid tumors induced in rats fed D&C Red No. 19 may have been produced by thyroid hormonal imbalance rather than by the direct carcinogenic action of the test compound, D&C Red No. 19. FDA finds that no data to support this position were submitted by CTFA and there was no request for a hearing on this contention. This subject was also discussed in detail in the **Federal Register** (51 FR 28351).

FDA, in the **Federal Register** of October 6, 1986 (51 FR 35509), published a final rule which removed the stay of the effective date for the permanent listing of D&C Red No. 19 and established the effective date of the permanent listing for use in externally applied drugs and cosmetics as October 6, 1986. In that rule, the Public Citizen's objections, which stated that the Delaney clause of the act unequivocally prohibits approval of a color additive (D&C Red No. 19), were evaluated by FDA and rejected. In rejecting the objections, FDA concluded that " \* \* \* under any reasonable standard, D&C Orange No. 17 and D&C Red No. 19 are safe for use in externally applied drugs and cosmetics and that the Delaney clause does not bar permanent listing of these color additives."

Following publication of the final rule establishing the effective date for D&C Red No. 19, which also rejected Public Citizen's objections to the rulemaking, Public Citizen filed suit in the U.S. Court of Appeals for the District of Columbia to overturn the FDA decision to permanently list the color additives D&C Orange No. 17 and D&C Red No. 19 (*Public Citizen v. Young*, No. 86-1548).

In the **Federal Register** of February 19, 1987 (52 FR 5081 and 52 FR 5083) FDA published clarifications to the preamble of the August 7, 1986, documents permanently listing D&C Red No. 19 and D&C Orange No. 17. These documents refined the position taken by FDA that the Delaney clause of the act did not apply to this situation. The documents

were summarized by the Court of Appeals as follows:

These notices effectively apply quantitative risk assessment at the stage of determining whether a substance "induce[s] cancer in man or animal". They assert that even where a substance does cause cancer in the conventional sense of the term, the FDA may find that it does not "induce cancer in man or animal" within the meaning of 21 U.S.C. [§] 376(b)(5)(B).

In an opinion dated October 23, 1987, the court issued its opinion regarding Public Citizen's challenge of FDA's decision to permanently list the color additives D&C Orange No. 17 and D&C Red No. 19.

In sum, we hold that the Delaney Clause of the Color Additive Amendments does not contain an implicit *de minimis* exception for carcinogens with trivial risk to humans. We based this decision on our understanding that Congress adopted an "extraordinarily rigid" position, denying the FDA authority to list a dye once it is found to "induce cancer in \* \* \* animals" in the conventional sense of the term, and, \* \* \* that the agency's *de minimis* interpretation of the Delaney Clause of the Color Additive Amendments is contrary to law. The listing decisions for D&C Orange No. 17 and D&C Red No. 19 based on that interpretation must therefore be corrected.

The U.S. Supreme Court subsequently refused to grant a writ of certiorari on the Appeals Court decision.

### III. Conclusions

FDA has reviewed the petition for D&C Red No. 19 in light of its finding that the color additive has been shown to induce cancer and the Court's decision that there is no *de minimis* exception to the Delaney anti-cancer clause. The agency concludes that there is no basis upon which to grant the petition. Therefore FDA denies the color additive petition to permanently list D&C Red No. 19 for use in externally applied drugs and cosmetics. This action is based not only upon previous findings by FDA that this color additive is carcinogenic in test animals, but on its continuing belief that those findings are correct. In addition, there are no scientific issues raised by CTFA that have not been addressed. Applying these findings to the decision of the U.S. Court of Appeals for the District of Columbia that D&C Red No. 19, which had been found to be a carcinogen in animals, cannot be listed as a color additive on externally applied drugs and cosmetics on the basis of a *de minimis* exception to section 706(b) of the act, FDA concludes that it must deny the petition.

In a final rule published elsewhere in this issue of the **Federal Register**, FDA is

removing the regulations permanently listing D&C Red No. 19 for use in externally applied drugs and cosmetics and removing the regulations that provide for the provisional use of its lakes. That final rule is referenced, along with the earlier **Federal Register** documents of February 4, 1983 (43 FR 5262), August 7, 1986 (51 FR 28346), October 6, 1986 (51 FR 35509) and February 19, 1987 (52 FR 5081).

Any person who will be adversely affected by this regulation may at any time on or before August 15, 1988, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the agency has received or lack thereof in the **Federal Register**.

This notice is issued under the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403 (21 U.S.C. 376 (b), (c), and (d) and the transitional provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86-618, sec. 203, 74 Stat. 404-407 (21 U.S.C. 376 note)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10).

Dated: July 12, 1988.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 88-16042 Filed 7-14-88; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 83C-0102]

**Color Additives; Denial of Petition for Listing of D&C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics**

**AGENCY:** Food and Drug Administration.  
**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is denying the color additive petition to permanently list D&C Orange No. 17 for use in externally applied drugs and cosmetics. This action is based upon previous findings by FDA that this color additive is carcinogenic in test animals and the finding of the U.S. Court of Appeals for the District of Columbia that D&C Orange No. 17, which had been found to be a carcinogen in animals, cannot be listed as a color additive in externally applied drugs and cosmetics on the basis of a *de minimis* exception to section 706(b) of the Federal Food, Drug, and Cosmetic Act (the act). In a final rule published elsewhere in this issue of the *Federal Register*, FDA is removing the regulations permanently listing D&C Orange No. 17 for use in externally applied drugs and cosmetics and removing the regulations that provide for the provisional use of its lakes.

**DATE:** Objections by August 15, 1988.

**ADDRESS:** Written objections may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Gerard L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

**SUPPLEMENTARY INFORMATION:**

**I. Introduction**

D&C Orange No. 17, which has been in use for many years, is the chemical 1-[[2,4-dinitrophenyl]azo]-2-naphthalenol (CAS Reg. No. 3468-63-1). Because D&C Orange No. 17 was in use at the time the Color Additive Amendments of 1960 were enacted, it was provisionally listed for drug and cosmetic use in the *Federal Register* of October 12, 1960 (25 FR 9759).

**II. Regulatory History**

D&C Orange No. 17 is the subject of a color additive petition (CAP 9C0090) that was submitted by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1100 Vermont Ave. NW., Washington, DC 20005) on April 14, 1969. The petition requested the

permanent listing of D&C Orange No. 17 for coloring lipsticks, ingested drugs and cosmetics, and externally applied drugs and cosmetics. The petition was amended on May 14, 1974, to include the listing of D&C Orange No. 17 for eye-area use.

In the *Federal Register* of February 4, 1977 (44 FR 6992), FDA published revised provisional regulations which required new chronic toxicity studies on 31 color additives, including D&C Orange No. 17, as a condition for the continued provisional listing of these color additives.

In the *Federal Register* of April 1, 1983 (48 FR 14045), FDA published a notice denying that portion of CAP 9C0090 dealing with ingested uses of D&C Orange No. 17 in drugs and cosmetics and withdrawing that portion of the petition that requested listing of D&C Orange No. 17 for eye area use. (Also published in the April 1, 1983, issue of the *Federal Register* (48 FR 13976) was a final regulation extending the provisional listing of D&C Orange No. 17 for use in externally applied drugs and cosmetics.) The denial was based upon a finding by FDA that D&C Orange No. 17 was a carcinogen when ingested by test animals. The rationale for this decision is stated in the *Federal Register* document of April 1, 1983. CTFA did not object to the denial.

In the *Federal Register* of August 7, 1986 (51 FR 28331), FDA published a final regulation permanently listing D&C Orange No. 17 for use in externally applied drugs and cosmetics. In the August 7, 1986, document FDA concluded that the results of chronic toxicity studies demonstrate that D&C Orange No. 17 is carcinogenic when administered in the diet to laboratory mice and rats. Specifically the agency concluded from the data that dietary exposure to D&C Orange No. 17 produced the carcinogenic effect of a statistically significant increase in the number of female rats with hepatocellular neoplasms as compared to the control groups. Moreover, the agency determined that D&C Orange No. 17 exposure in long-term feeding studies in mice was associated with a statistically significant dose-related increase in the number of male mice with hepatocellular neoplasms as compared to the control groups.

In its submissions, CTFA presented several arguments that raised questions about the relevance of the ingestion studies to a determination of the safety of the external uses of D&C Orange No. 17. The entire discussion of FDA's determination that the color additive induced cancer in animals, including FDA's response to issues raised by

CTFA, as summarized below, appeared in the listing document of August 7, 1986 (51 FR 28331).

*A. Interpretation of Maximum Tolerated Dose*

CTFA asserted that the dose level of the second rat study substantially exceeded the maximum tolerated dose and violated the National Cancer Institute (NCI) guidelines for carcinogenicity testing. However, in summary, the agency concluded that, for the female rats, the maximum tolerated dose was not exceeded and the CTFA's contention that the study violated NCI guidelines for carcinogenicity testing was not substantiated.

*B. Significance of Mouse Liver Tumors*

CTFA questioned the significance of the mouse liver tumors observed in the chronic test. FDA's Cancer Assessment Committee reviewed the data and CTFA's arguments and reached the following conclusion: CTFA's argument about the high background incidence of liver cancer in mice does not apply to the CD-1 mouse, the strain used in the mouse study. Moreover, CTFA's argument that the maximum tolerated dose was exceeded is misplaced. In the absence of any observed significant treatment-related effects in the high-dose male mouse group in which the increase in hepatocellular neoplasms was observed, the Cancer Assessment Committee concluded that the maximum tolerated dose was not exceeded in the study. Finally, CTFA's arguments concerning the limited statistical significance associated with the male mouse liver tumors were evaluated. The Cancer Assessment Committee noted that the tumor incidence in treated mice was greater than the historical control values and concluded that the hepatocellular tumors observed in the male mice were the result of the ingestion of D&C Orange No. 17. Although a scientific review panel of the U.S. Public Health Service scientists reached different conclusions with respect to the mouse bioassay, the agency concluded that this difference was inconsequential in light of the results of the rat feeding study.

*C. Mechanism of Carcinogenicity and Significance of "Benign" Tumors*

In its submissions, CTFA offered the following arguments concerning the significance of benign tumors: "[In the female rat] only the incidence of benign hepatocellular adenomas (neoplastic nodules) was increased. There was no significant increase in the incidence of malignant carcinomas in the treated

females. Nor was there any effect in the males fed the same level of the color additive. This indicates a very weak effect apparently occurring only at high doses that are toxic to the liver. This suggests an indirect mechanism of neoplasia secondary to toxic damage." In summary, the FDA response stated that the data lead the agency to conclude that D&C Orange No. 17 most likely exhibits a primary effect. CTFA has offered no evidence to the contrary. CTFA also suggested in its submission that the female rat liver tumors in the 1 percent dose group are caused by an "indirect mechanism of neoplasia secondary to toxic damage \* \* \*". However, FDA noted that CTFA had not submitted any scientific evidence to support such a hypothesis.

In the document listing this color, FDA concluded, on the basis of its evaluation of the data for the color additive, that although studies established that the color additive caused cancer in animals, quantitative risk assessment of the color indicated that the risk of human cancer from its use in externally applied drugs and cosmetics would be extremely low, and that there would be no benefit to the public from prohibiting these uses of the color additive. Thus, FDA concluded that the use of D&C Orange No. 17 in externally applied drugs and cosmetics was safe under the conditions of use prescribed in the regulations permanently listing the color additive.

FDA also concluded that it was appropriate for the agency to apply a *de minimis* exception to the Delaney clause of the act where the color additive imposes essentially no additional risk of cancer to the public; that any risk the color additive may present is of no public health consequence; and that, under these circumstances, the Delaney clause does not require a ban of the externally applied uses of D&C Orange No. 17.

In response to the permanent listing of D&C Orange No. 17, the Public Citizen Litigation Group (Public Citizen) filed objections on August 21, 1986, which stayed the effective date of the regulation. However, Public Citizen did not request a hearing. Additionally, on September 8, 1986, CTFA filed comments in support of the FDA's permanent listing of D&C Orange No. 17.

The CTFA comments specifically stated that CTFA supported the permanent listing of the color additive. The comments did not represent objections to the listing rule. In the introduction to its comments, however, CTFA asserted that some cancer experts consider the liver of the inbred mouse to be an invalid system for carcinogenicity testing and the comments stated that

these experts considered mouse liver tumors to be of limited relevance to human risk because of the extreme sensitivity of the mouse liver to chemical insult. FDA finds that CTFA's arguments on this subject were discussed in detail in the *Federal Register* in the listing document (51 FR 28335 and 28336). CTFA did not present any new data in support of its position and did not request a hearing on the subject.

Additionally, CTFA also commented, in the case of the female rat liver tumors, that the tumors were benign and found only at a high feeding level that probably exceeded the maximum tolerated dose. CTFA further stated that the female rat liver data suggest an indirect mechanism for causing tumors that was secondary to toxic damage, which could not occur in humans because they would never be exposed to such high levels of D&C Orange No. 17. FDA finds that CTFA's safety arguments on this issue were also addressed in detail in the *Federal Register* (51 FR 28331). Additionally, CTFA has at no time submitted data in support of its speculation that such a secondary mechanism may occur.

FDA, in the *Federal Register* of October 6, 1986 (51 FR 35509), published a final rule which removed the stay of the effective date for the permanent listing of D&C Orange No. 17 and established the effective date of the permanent listing for use in externally applied drugs and cosmetics as of October 6, 1986. In that rule, Public Citizen's objections, which stated that the Delaney clause of the act unequivocally prohibits approval of a color additive (D&C Orange No. 17), were evaluated by FDA and rejected. In rejecting the objections, FDA concluded that " \* \* \* under any reasonable standard, D&C Orange No. 17 and D&C Red No. 19 are safe for use in externally applied drugs and cosmetics and that the Delaney clause does not bar the permanent listing of these color additives."

Following publication of the final rule establishing the effective date for D&C Orange No. 17, which also rejected Public Citizen's objections to the rulemaking, Public Citizen filed suit in the U.S. Court of Appeals for the District of Columbia to overturn the FDA decision to permanently list the color additives D&C Orange No. 17 and D&C Red No. 19 (*Public Citizen v. Young*, No. 86-1548).

In the *Federal Register* of February 19, 1987 (52 FR 5081 and 52 FR 5083) FDA published clarifications to the preamble of the August 7, 1986, documents permanently listing D&C Red No. 19 and

D&C Orange No. 17. These documents refined the position taken by FDA that the Delaney clause of the act did not apply to this situation. The clarification documents were summarized by the Court of Appeals as follows:

These notices effectively apply quantitative risk assessment at the stage of determining whether a substance "induce[s] cancer in man or animal". They assert that even where a substance does cause cancer in the conventional sense of the term, the FDA may find that it does not "induce" cancer in man or animal" within the meaning of 21 U.S.C. [§] 376(b)(5)(B).

In an opinion dated October 23, 1987, the court issued its opinion regarding the Public Citizen challenge of the decision by FDA to permanently list the color additives D&C Red No. 19 and D&C Orange No. 17:

In sum, we hold that the Delaney Clause of the Color Additive Amendments does not contain an implicit *de minimis* exception for carcinogens with trivial risk to humans. We based this decision on our understanding that Congress adopted an "extraordinarily rigid" position, denying the FDA authority to list a dye once it is found to "induce cancer in \* \* \* animals" in the conventional sense of the term, and, \* \* \* that the agency's *de minimis* interpretation of the Delaney Clause of the Color Additive Amendments is contrary to law. The listing decisions for D&C Orange No. 17 and D&C Red No. 19 based on that interpretation must therefore be corrected.

The U.S. Supreme Court subsequently refused to grant a writ of certiorari on the Appeals Court decision.

### III. Conclusions

FDA has reviewed the petition for D&C Orange No. 17 in light of its finding that the color additive has been shown to induce cancer and the Court's decision that there is no *de minimis* exception to the Delaney anti-cancer clause. The agency concludes that there is no basis upon which to grant the petition. Therefore FDA denies the color additive petition to permanently list D&C Orange No. 17 for use in externally applied drugs and cosmetics. This action is based not only upon previous findings by FDA that this color additive is carcinogenic in test animals, but on its continuing belief that those findings are correct. In addition, there are no scientific issues raised by CTFA that have not been addressed. Applying these findings to the decision of the U.S. Court of Appeals for the District of Columbia that D&C Orange No. 17, which had been found to be a carcinogen in animals, cannot be listed as a color additive in externally applied drugs and cosmetics on the basis of a *de minimis* exception to section 706(b) of

the act, FDA concludes that it must deny the petition.

In a final rule published elsewhere in this issue of the **Federal Register**, FDA is removing the regulations permanently listing D&C Orange No. 17 for use in externally applied drugs and cosmetics and removing the regulation that provides for the provisional use of its lakes. That final rule is referenced, along with the earlier **Federal Register** documents of April, 1983 (48 FR 14045), August 7, 1986 (51 FR 28331), October 6, 1986 (51 FR 35509) and February 19, 1987 (52 FR 5081).

Any person who will be adversely affected by this regulation may at any time on or before August 15, 1988, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the agency has received or lack thereof in the **Federal Register**.

This notice is issued under the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403 (21 U.S.C. 376 (b), (c), and (d)) and the transitional provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86-618, sec. 203, 74 Stat. 404-407 (21 U.S.C. 376 note)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10).

Dated: July 12, 1988.

John M. Taylor,  
Associate Commissioner for Regulatory  
Affairs.

[FR Doc. 88-16043 Filed 7-14-88; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 83C-0127]

**Color Additives; Denial of Petition for Listing of D&C Red No. 8 and D&C Red No. 9 for Use in Ingested Drug and Cosmetic Lip Products and in Externally Applied Drugs and Cosmetics**

**AGENCY:** Food and Drug Administration.  
**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is denying the color additive petition to permanently list D&C Red Nos. 8 and 9 for use in ingested drugs and cosmetic lip products and in externally applied drugs and cosmetics. This action is based upon previous findings by FDA that these color additives are carcinogenic in test animals and on the decision of the U.S. Court of Appeals for the District of Columbia on D&C Orange No. 17 and D&C Red No. 19 that carcinogenic color additives cannot be listed as color additives on the basis of a *de minimis* exception to the color additive Delaney clause in the Federal Food, Drug, and Cosmetic Act (the act). In a final rule, published elsewhere in this issue of the **Federal Register**, FDA is removing the regulations permanently listing D&C Red Nos. 8 and 9 for use in ingested drugs and cosmetic lip products and in externally applied drugs and cosmetics and removing the regulations that provide for the provisional use of their lakes.

**DATE:** Objections by August 15, 1988.

**ADDRESS:** Written objections may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Gerard L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

**SUPPLEMENTARY INFORMATION:**

**I. Introduction**

D&C Red Nos. 8 and 9 have been in use for many years. D&C Red No. 8 is principally the monosodium salt of 5-chloro-2-[[2-hydroxy-1-naphthalenyl]azo]-4-methylbenzenesulfonic acid (CAS Reg. No. 2092-56-0). D&C Red No. 9 is

principally the barium salt (1:2) of 5-chloro-[[2-hydroxy-1-naphthalenyl]azo]-4-methylbenzenesulfonic acid (CAS Reg. No. 5160-2-1). Because D&C Red Nos. 8 and 9 were in use at the time the Color Additive Amendments of 1960 (the amendments) were enacted, they were provisionally listed for drug and cosmetic use in the **Federal Register** of October 12, 1960 (25 FR 9759).

**II. Regulatory History**

D&C Red Nos. 8 and 9 have been the subject of a color additive petition (CAP 5C0028), submitted by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1100 Vermont Ave. NW., Washington, DC 20005) on May 17, 1965. The petitioner has requested the permanent listing of D&C Red Nos. 8 and 9 for use generally in coloring drugs and cosmetics.

In the **Federal Register** of February 4, 1977 (44 FR 6991), FDA published revised provisional regulations which required new chronic toxicity studies on 31 color additives, including D&C Red Nos. 8 and 9, as a condition to the continued provisional listing of these color additives.

In the **Federal Register** of December 5, 1986 (51 FR 43877), FDA published a final rule permanently listing D&C Red Nos. 8 and 9 for use in ingested drug and cosmetic lip products and in externally applied drugs and cosmetics. In the December 5, 1986, document, FDA concluded that the results of chronic toxicity studies demonstrate that D&C Red No. 9 is carcinogenic when administered in the diet of laboratory rats. Specifically, the agency concluded from the data that dietary exposure to D&C Red No. 9 is associated with an increase in the occurrence of splenic cancer in male rats and, thus, that D&C Red No. 9 induces cancer when tested in laboratory animals. As discussed in the final rule (51 FR 43877), D&C Red No. 8 has not been tested in a chronic feeding study, but FDA has concluded that, for the purpose of assessing safety, D&C Red No. 8 and D&C Red No. 9 are toxicologically equivalent. The petitioner has agreed with this conclusion. Thus, the agency has concluded that D&C Red No. 8 is also a carcinogen and that action on both of these color additives can be taken on the basis of the results of chronic studies on D&C Red No. 9.

The December 5, 1986, final rule permanently listing D&C Red Nos. 8 and 9 also responded to CTFA's arguments in support of its petition. In its submission in support of its petition, CTFA raised questions about the