

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR PARTS 74, 81, AND 82

[DOCKET NO. 82N-0268] **CF 76N-0366**

D&C ORANGE NO. 5

AGENCY: Food and Drug Administration.

47FR49632
11-2-82

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is permanently listing D&C Orange No. 5 for use in lipsticks or other lip cosmetics and in drug and cosmetic mouthwashes and dentifrices.

This action is a partial response to a petition filed by the Cosmetic, Toiletry, and Fragrance Association, Inc. (CTFA).

This final rule will remove D&C Orange No. 5 from the

provisional list of color additives. However, to provide an opportunity for objections, published elsewhere in this issue of

~~the FEDERAL REGISTER is an order that extends the closing date~~

for the provisional listing of D&C Orange No. 5 for use in

lipsticks and other lip cosmetics and in drug and cosmetic

mouthwashes and dentifrices. In addition, that order terminates

the provisional listing of this color additive for use in

externally applied drugs and cosmetics. This final rule also

Cancels certificates for D&C Orange No. 5 for use in externally applied drugs and cosmetics.

DATES: Effective November 30, 1982; objections by November 29, 1982; Certificates cancelled effective October 29, 1982.

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.

*11-29-82
eff 11-30-82*

FOR FURTHER INFORMATION CONTACT:

Andrew D. Laumbach,
Bureau of Foods (HFF-334),
Food and Drug Administration,
200 C St. SW.,
Washington, DC 20204,
202-472-5690.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of August 6, 1973 (38 FR 21199), FDA announced that a petition (CAP 660041) for the permanent listing of D&C Orange No. 5 as a color additive for general use in drugs and cosmetics had been filed by the Toilet Goods Association, Inc. (now CTFA, c/o Hazleton Laboratories, Inc., 9200 Leesburg Turnpike, Vienna, VA 22180). The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376).

In the FEDERAL REGISTER of October 12, 1960 (25 FR 9759), as amended August 16, 1961 (26 FR 7578), and December 30, 1970 (35 FR 19749), FDA established temporary tolerances under § 81.25 (21 CFR 81.25), formerly § 8.503 (21 CFR 8.503), for the use of certain provisionally listed color additives, including D&C Orange No. 5, in lipsticks, ingested drugs, and other products subject to ingestion, such as mouthwashes and dentifrices. The agency set tolerance limits because "subacute studies have established that these colors are toxic substances, unsafe for unrestricted use in drugs and cosmetics" (25 FR 9760).

The original temporary tolerance levels for these color additives were based on preliminary usage information and toxicological information from testing performed in the 1950's. Later, color additive petitions were submitted that contained information concerning the use of each of the color additives, as well as reports on chronic feeding studies with each of the color additives. In addition, in accordance with a regulation published in the FEDERAL REGISTER of September 11, 1971 (36 FR 18336) (amended June 12, 1973; 38 FR 15472), teratology and multigeneration reproduction studies were conducted with the color additives listed under temporary tolerances. The data from these three sources provided a more substantive base for determining appropriate levels of use for the color additives requiring temporary tolerances. On the basis of these data, in a regulation published in the FEDERAL REGISTER of August 21, 1979 (44 FR 48964), FDA established the current temporary tolerances for D&C Orange No. 5, which appear in § 81.25 and which no longer permit use of D&C Orange No. 5 in ingested drugs.

TOXICOLOGICAL TESTING OF D&C ORANGE NO. 5

The provisional regulations published in the FEDERAL REGISTER of February 4, 1977 (42 FR 6992) required new chronic toxicity studies for D&C Orange No. 5 as a condition of its continued provisional listing for ingested uses. FDA required these studies for 31 color additives because the toxicity studies the petitioners had submitted to support the safe use of these color additives were deficient in several respects. FDA described these deficiencies in the FEDERAL REGISTER of September 23, 1976 (41 FR 41863):

1. Many of the studies were conducted using groups of animals, i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn on the chronic toxicity or carcinogenic potential of the color. The small number of animals used does not, in of itself, cause this result; but when considered together with the other deficiencies in this listing, it does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.

2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.

3. In a number of the studies, an insufficient number of animals was reviewed histologically.

4. In a number of the studies, insufficient numbers of tissues were examined in those animals selected for pathology.

5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

FDA postponed the closing date for the provisional listing of these color additives until January 31, 1981, to permit the completion of required chronic toxicity studies. However, in response to 3 petitions to provide for timely completion of the ongoing studies and submission of data to FDA on a prescribed schedule, the agency extended the closing dates for 23 provisionally listed color additives under test, including D&C Orange No. 5, on March 27, 1981 (46 FR 18954). The current closing date for the provisional listing of D&C Orange No. 5 is October 30, 1982.

Published elsewhere in this issue of the FEDERAL REGISTER is an order that extends the closing date for the provisional listing of D&C Orange No. 5 for use in lipsticks or other lip cosmetics and in drug and cosmetic mouthwashes and dentifrices. The new closing date for D&C Orange No. 5 is being established to provide for receipt and evaluation of any objections submitted in response to this final rule for permanent listing. The agency

advises that it is not extending the closing date for use of D&C Orange No. 5 in externally applied drugs and cosmetics because this final rule does not provide for such uses. The provisional listing in § 81.1(b) (21 CFR 81.1(b)) of D&C Orange No. 5 for the permitted uses will be removed when this listing rule becomes effective.

EVALUATION OF THE SAFETY OF D&C ORANGE NO. 5

Under section 706(b)(4) of the act (21 U.S.C. 376(b)(4)), the so-called "general safety clause" for color additives, a color additive cannot be listed for a particular use unless the data presented to FDA establish that the substance is safe for that use. Although what is meant by "safe" is not explained in the general safety clause, the legislative history makes clear that this word is to have the same meaning for color additives as for food additives. (See H. Rep. No. 1761, "Color Additive Amendments of 1960," Committee on Interstate and Foreign Commerce, 86th Cong., 2d Sess. 11 (1960).) The Senate report on the Food Additives Amendment of 1958 states:

The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not--and

cannot--require proof beyond any possible doubt that no harm will result under any conceivable circumstance. This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance.

S. Rep. No. 2422, "Food Additives Amendment of 1958," Committee on Labor and Public Welfare, 85th Cong., 2d Sess. 6 (1958).

FDA has incorporated this concept of safety into its color additive regulations. Under 21 CFR 70.3(i), a color additive is "safe" if "there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive." Therefore, the general safety clause prohibits approval of a color additive if doubts about the safety of the additive for a particular use are not resolved to an acceptable level in the minds of competent scientists.

The agency has now completed its evaluation of the color additive petition for D&C Orange No. 5, which included two new chronic toxicity studies in rats and mice. These new long-term chronic studies represent current state-of-the-art toxicological testing. The protocols for these studies have benefited from knowledge of deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity protocols. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of the two species tested significantly increases the power of these tests to detect dose-related effects. The studies were designed and conducted in full compliance with the good laboratory practice regulations and were subject to inspections by FDA officials during their course.

Based on the evaluation of the results of the two new chronic toxicity studies, the agency has determined that D&C Orange No. 5 is not carcinogenic to Charles River Sprague-Dawley CD rats or CD-1 mice after lifetime dietary exposure as high as 1.0 percent and 0.5 percent, respectively, under conditions of testing adequate to provide assurance of its safe use.

In evaluating the safety of this color additive, the agency has evaluated other appropriate animal studies in addition to these new chronic studies to determine any potential adverse effects from the use of D&C Orange No. 5 and thus to determine

the level at which exposure to the color additive can be considered safe. The agency makes the latter determination by establishing a "no-adverse-effect" level on the basis of each animal study, by applying a safety factor to each study, and by selecting the study that leads to a calculation of the lowest acceptable daily intake.

For D&C Orange No. 5, FDA has evaluated the two new chronic feeding studies in rats and mice, chronic toxicity studies in dogs and rats, a teratology study in rats, a three-generation reproduction study in rats, a short-term feeding study in rabbits, an 18-month skin painting study in mice, and a dermal study in rabbits. From these evaluations, the agency has concluded that the rabbit feeding study establishes the lowest acceptable daily intake for D&C Orange No. 5. In the rabbit feeding study, the agency found increased intrauterine deaths (resorptions) at the high dose of 160 milligrams per kilogram of body weight (mg/kg) and a no-adverse-effect level of 50 mg/kg. FDA has applied a conservative thousandfold safety factor to the 50 mg/kg/day no-adverse-effect level to calculate an acceptable daily intake of 0.05 mg/kg/day or 3 mg/day for a 60-kg person. FDA applied a thousandfold safety factor, rather than the hundredfold factor set forth in 21 CFR 70.40, because the agency's calculation is based upon the results from a

short-term test, and the agency's general practice is to apply a thousandfold safety factor to the results of such short-term tests unless there are specific reasons to do otherwise. Similarly, because of its reliance on the short-term test, the agency has compared the acceptable daily intake to estimated short-term use rather than average chronic use of the color additive.

The agency generally considers a color additive as safe under its intended conditions of use if the estimated daily intake of the additive does not exceed its acceptable daily intake. In determining the estimated daily intake, FDA has concentrated on the high users in the total population and on the maximum estimated exposure of this population to known and probable uses of the color additive. The agency has developed the following estimates for maximum exposure under various use categories: ingested drugs (not currently allowed), 24 mg/day;

external drugs, 2.4 mg/day; lipsticks (6 percent color additive), 3.0 mg/day; mouthwashes and dentifrices, 0.2 mg/day; topical cosmetics, 2.0 mg/day. These estimates cannot be simply totaled to obtain a cumulative exposure because each estimate is a maximum, and it is unlikely that anyone would use all products at the potential maximum level on any given day. Nevertheless, it is clear that unrestricted use would permit exposure to D&C Orange No. 5 in excess of 3.0 mg/day. Therefore, because the major use of D&C Orange No. 5 has been in lipsticks, FDA is permanently listing the color additive for this use at levels of up to 5 percent in lipsticks and lip cosmetics (2.5 mg/day maximum). The agency is establishing the 5-percent maximum level, instead of the 6-percent in effect under the temporary tolerances, to assure that the acceptable daily intake is not exceeded. FDA is also permanently listing D&C Orange No. 5 for use in mouthwashes and dentifrices (0.2 mg/day maximum). At the same time, even though the agency recognizes that actual internal exposure to D&C Orange No. 5 from externally applied drugs and cosmetics may be less than estimated above, there are no data currently available that establish that FDA's exposure estimates are incorrect. Therefore, FDA is unable at this time to find that these external uses of D&C Orange No. 5 are safe, and consequently the agency is not listing the color additive for these uses.

CONCLUSION ON SAFETY

The agency concludes that D&C Orange No. 5 is safe under conditions of use set forth below, and that certification is necessary for the protection of the public health. The final toxicity study reports, the interim reports, and the agency's toxicology evaluations of these studies are on file at the Dockets Management Branch (address above). They may be reviewed there between 9 a.m. and 4 p.m., Monday through Friday.

The agency is not denying the color additive petition for D&C Orange No. 5 (CAP 6C0041) for ingested and externally applied drug and cosmetic use. As stated above, the agency recognizes that the estimated daily intake may be exaggerated. FDA encourages interested persons to provide information that the agency can use to determine the extent to which D&C Orange No. 5 is absorbed through the skin from the use of externally applied drugs and cosmetics. Therefore, the agency will accept and consider new information submitted in support of the permanent listing of the petitioned uses that cannot be approved at this time. If no further information is received by April 27, 1983, the agency will consider that portion of the petition for uses other than those subject to this final rule as withdrawn without prejudice under § 71.4 (21 CFR 71.4).

Certificates issued for D&C Orange No. 5, and its lakes, and all mixtures containing the color additive are cancelled and have no effect as pertains to its use in for externally applied drug and cosmetics after October 29, 1982. Use of the color additive in externally applied drugs or externally applied cosmetics after that date will cause such products to be adulterated within the meaning of the act (21 U.S.C. 301 et seq.), and the violation may be subject to regulatory action. This prohibition applies to the use of the straight color, its lakes, and color additive mixtures containing D&C Orange No. 5. The agency concludes that the protection of the public health does not require the removal from the market of drugs and cosmetics containing the color additive for external use or the destruction of drugs or cosmetics that are being manufactured to which the color additive has been added on or before October 29, 1982.

Manufacturers of new drugs and new animal drugs (including certifiable antibiotics for animal use) that may be externally applied and that contain D&C Orange No. 5 may either cease adding the color additive or substitute a different color in accordance with the provisions of § 314.8(d)(3) and (e) or § 514.8(d)(3) and (e) (21 CFR 314.8(d)(3) and (e) or 514.8(d)(3) and (e)), as appropriate. If a substitute color is used, the manufacturer shall file with FDA a supplemental new

drug application or supplemental new animal drug application, which contains data describing the new composition and showing that the change in composition does not interfere with any assay and control procedures used in manufacturing the drug, or that the assay and control procedures used in manufacturing the drug have been revised to make them adequate. The applicant shall also submit data that establish the stability of the revised formulation or, if the data are too limited to support a conclusion that the drug will retain its declared potency for the reasonable marketing period, a commitment to test the stability of marketed batches at reasonable intervals, to submit the data as they become available, and to recall from the market any batch found to fall outside the approved specification for the drug.

Each sponsor of a notice of claimed investigational exemption for a new drug (IND) or a notice of claimed investigational exemption for a new animal drug (INAD) containing the subject color should promptly amend the IND or INAD to indicate that the color additive has been removed or a different color additive substituted.

The agency is aware that supplies of alternative color additives may be difficult to obtain immediately. Consequently, drug and cosmetic labeling that states that the product contains "artificial color" or that specifically identifies D&C Orange No. 5 may continue to be used with uncolored products, or

products containing substitute colors, during the time necessary to obtain supplies of revised labeling or until November 2, 1983, whichever occurs first.

The agency is establishing new chemical specifications that identify the color additive more precisely than those specifications currently in Part 82. Also, the chemical name for the color additive in the new listing under Part 74 (21 CFR Part 74) is different from the name currently listed under Part 82 (21 CFR Part 82) and from the "Chemical Abstracts" designations. The agency has decided to follow the nomenclature commonly used in the chemical literature, where the color additive is referred to as a fluorescein derivative.

The agency concludes that it is necessary to include in the ~~listing regulation for D&C Orange No. 5 a brief description of~~ the manufacturing process to ensure the safety of the color additive. The agency is concerned that the color additive may contain potentially toxic substances dependent upon the manufacturing process used to produce the color additive. The agency is not able at this time to set specifications which would preclude their presence. The agency has contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to develop appropriate specifications for color

additives for use in food as part of the Food Chemicals Codex. Similarly, appropriate specifications for color additives for use in drugs and cosmetics will be developed following the general guidelines used by NAS/NRC in its evaluation of color additives used in food. The agency concludes that specifying, through a general description, the manufacturing process in the regulation for the color additive will provide an adequate assurance of safety until suitable specifications can be developed. Production of the color additive by the specified method will assure qualitatively similar batches and thus adequately assure the absence of unanticipated potentially toxic impurities.

The agency has determined under 21 CFR 25.24(b)(12) and (d)(5) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR

Part 74: Color additives; Color additives subject to certification; Cosmetics; Drugs.

Part 81: Color additives; Color additives provisional list; Cosmetics; Drugs.

Part 82: Color additives; Color additives lakes; Color additives provisional list; Cosmetics; Drugs.

Therefore, under 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 authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Parts 74, 81, and 82 are amended as follows:

~~PART 74--LISTING OF COLOR ADDITIVES~~
~~SUBJECT TO CERTIFICATION~~

1. Part 74 is amended:

a. By adding new § 74.1255 to Subpart B, to read as follows:

§ 74.1255. D&C Orange No. 5

(a) Identity. (1) The color additive D&C Orange No. 5 is a mixture consisting principally of 4',5'-dibromofluorescein (CAS Reg. No. 596-03-2) and 2',4',5'-tribromofluorescein (CAS Reg. No. 25709-83-5) and 2',4',5',7'-tetrabromofluorescein (CAS Reg. No. 15086-94-9). D&C Orange No. 5 is manufactured by brominating fluorescein with elemental bromine. The fluorescein is manufactured by the acid condensation of resorcinol and phthalic acid or its anhydride. The fluorescein is isolated and partially purified prior to bromination.

(2) Color additive mixtures for drug use made with D&C Orange No. 5 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter as safe for use in color additive mixtures for coloring drugs.

(b) Specifications. D&C Orange No. 5 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice:

4',5'-Dibromofluorescein, not less than 50 percent and not more than 65 percent.

2',4',5'-Tribromofluorescein, not less than 30 percent and not more than 40 percent.

2',4',5',7'-Tetrabromofluorescein, not more than 10 percent.

Sum of 2',4'-dibromofluorescein and 2',5'-dibromofluorescein, not more than 2 percent.

4'-Bromofluorescein, not more than 2 percent.

Fluorescein, not more than 1 percent.

Phthalic acid, not more than 1 percent.

2-(3,5-Dibromo-2,4-dihydroxybenzoyl) benzoic acid, not more than 0.5 percent.

Brominated resorcinol, not more than 0.4 percent.

Sum of volatile matter (at 135° C) and halides and sulfates (calculated as sodium salts), not more than 10 percent.

Insoluble matter (alkaline solution), not more than 0.3 percent.

Lead (as Pb), not more than 20 parts per million.

Arsenic (as As), not more than 3 parts per million.

Mercury (as Hg), not more than 1 part per million.

Total color, not less than 90 percent.

(c) Uses and restrictions. D&C Orange No. 5 may be safely used for coloring mouthwashes and dentifrices that are ingested drugs in amounts consistent with current good manufacturing practice.

(d) Labeling. The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) Certification. All batches of D&C Orange No. 5 shall be certified in accordance with regulations in Part 80 of this chapter.

~~By adding new § 74.2255 to Subpart C, to read as follows:~~

§ 74.2255 D&C Orange No. 5.

(a) Identity and specifications. The color additive D&C Orange No. 5 shall conform in identity and specifications to the requirements of § 74.1255(a)(1) and (b).

(b) Uses and restrictions. D&C Orange No. 5 may be safely used for coloring mouthwashes and dentifrices that are ingested cosmetics in amounts consistent with current good manufacturing practice. D&C Orange No. 5 may be safely used for coloring lipsticks and other cosmetics intended to be applied to the lips in amounts not exceeding 5.0 percent by weight of the finished cosmetic products.

(c) Labeling requirements. The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) Certification. All batches of D&C Orange No. 5 shall be certified in accordance with regulations in Part 80 of this chapter.

PART 81--GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS
FOR PROVISIONAL COLOR ADDITIVES FOR USE IN
FOODS, DRUGS, AND COSMETICS

2. Part 81 is amended:

§ 81.1 [Amended]

a. In § 81.1 Provisional lists of color additives, by removing the entry for "D&C Orange No. 5" in paragraph (b).

§ 81.25 [Amended]

b. In § 81.25 Temporary tolerances, by removing the entries for "D&C Orange No. 5" in paragraphs (a)(1) and (b)(1)(i).

§ 81.27 [Amended]

c. In § 81.27 Conditions of provisional listing, by removing the entry for "D&C Orange No. 5" in paragraph (d).

d. In § 81.30 by adding new paragraph (q), to read as follows:

§ 81.30 Cancellation of certificates.

* * * * *

(q)(1) Certificates issued for D&C Orange No. 5, its lakes, and all mixtures containing the color additive are cancelled and have no effect as pertains to its use in externally applied drugs and cosmetics after October 29, 1982. and use of the color additive in the manufacture of externally applied drugs or cosmetics after this date will result in adulteration.

(2) The agency finds, on the basis of the scientific evidence before it, that no action has to be taken to remove from the market drugs and cosmetics to which the color additive was added on or before October 29, 1982.

PART 82--LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

3. Part 82 is amended by revising § 82.1255, to read as follows:

§ 82.1255 D&C Orange No. 5.

The color additive D&C Orange No. 5 shall conform in identity and specifications to the requirements of § 74.1255 (a)(1) and (b) of this chapter.

Any person who will be adversely affected by the foregoing regulation may at any time on or before November 29, 1982, file with the Dockets Management Branch (address above) written objections thereto. Objections shall show wherein the person filing will be adversely affected by the regulation, specify with particularity the provisions of the regulation deemed objectionable, and state the grounds for the objections. Objections shall be filed in accordance with the requirements of 21 CFR 71.30. If a hearing is requested, the objection shall state the issues for the hearing and shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents

shall be filed and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulations may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation shall become effective November 30, 1982, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the FEDERAL REGISTER.

(Sec. 706(b), (c), and (d), 74 Stat. 399-403 (21 U.S.C. 376(b), (c), and (d); sec. 203, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 376, note).)

Dated: OCT 28 1982

OCT 28 1982



Mark Novitch
Acting Commissioner of
Food and Drugs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

