DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 135]

[Docket No. FDC-60]

COLOR CERTIFICATION

NOTICE OF PROPOSED RULE MAKING

In the matter of amending §§ 135.3, 135.5, and 135.11 of the color-certification regulations:

It is proposed that, by virtue of the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 406 (b) 504, 604, 701, 52 Stat. 1049, 1052, 1055; 21 U. S. C. 346 (b) 354, 364, 371, 67 Stat. 18) and upon the basis of substantial evidence received at the public hearing held pursuant to the notice published in the FEDERAL REGISTER on December 19, 1953 (18 F R. 8600) and upon consideration of the briefs filed thereafter, the following order be made:

Findings of fact.[1] 1. After a hearing held beginning February 6, 1939, concerning regulations for certification of coal-tar colors, the coal-tar color now listed as FD&C Orange No. 1 (monosodium salt of 4-*p*-sulfophenylazo-1-naphthol) and the coal-tar color now listed as FD&C Orange No. 2 (1-*o*-tolylazo-2-naphthol) were found to be harmless and suitable for use in food, drugs, and cosmetics. After a hearing held beginning on July 5, 1939, concerning amendment of the coal-tar color regulations, the coal-tar color now listed as FD&C Red No. 32. (1-xylylazo-2-naphthol) was found to be harmless and suitable for use in food, drugs, and cosmetics. In accordance with these findings, these three colors, among others, were listed with appropriate specifications of identity and quality in the coal-tar color regulations (21 CFR 135.3) as certifiable for use in food, drugs, and cosmetics. (4 F. R. 1922, 1926, 1937, 3931, 3936, 3937; R. 46)

2. Because of advances in knowledge and techniques in the field of pharmacology, the Food and Drug Administration has initiated new tests to explore more fully the toxicity of the certifiable coal-tar colors. This involves the application of all techniques and procedures now considered necessary to assure proper evaluation. A number of these tests, with present-day techniques and procedures, have been conducted by the Division of Pharmacology of the Food and Drug Administration, using FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32.

Tests that have been terminated are:

a. FD&C Orange No. 1.

i. Chronic feeding tests in rats with diets containing 0.1, 0.5, 1, and 2 percent.

ii. Chronic oral administration to dogs at doses of 5 milligrams per kilogram of body weight and 100 milligrams per kilogram of body weight.

iii. Cathartic tests in dogs, using single oral dose.

b. FD&C Orange No. 2:

i. Chronic feeding tests in rats with diets containing 0.01, 0.05, 0.1, 0.2, and 0.25 percent.

ii. Tests designed to determine carcinogenicity in rats, using weekly subcutaneous injections of 0.1 milliliter of a 5-percent suspension. (The test was discontinued after 8 injections, because of toxicity.)

iii. Carcinogenicity tests in mice, using subcutaneous implantation of 12.1 milligrams at intervals for 30 to 55 weeks.

iv. Chronic oral administration to dogs at doses of 5, 20, and 100 milligrams per kilogram of body weight per day.

v. Chronic feeding tests in dogs at dietary levels of 0.2 percent and 0.04 percent.

vi. Cathartic tests in dogs, using single oral dose.

c. FD&C Red No. 32:

i. Chronic feeding tests in rats, with diets containing 0.1 percent.

ii. Subacute feeding tests in rats, with diets containing 0.25, 0.5, 1, and 2 percent.

iii. Chronic feeding tests in rats, with diets containing 0.1 percent and 0.25 percent.

iv. Carcinogenicity tests in rats, using weekly subcutaneous injections of 0.1 cubic centimeter to 0.2 cubic centimeter of a 5-percent suspension. (A second experiment, using weekly subcutaneous injections of 0.1 cubic centimeter of a 1-percent suspension, was discontinued after 8 injections, because of toxicity observed in rats receiving FD&C Orange No. 2 in another part of this experiment.)

v. Carcinogenicity tests in mice, using subcutaneous implantation of 10.8 milligrams at intervals for 35 weeks to 47 weeks.

vi. Chronic oral administration to dogs at doses of 5, 20, and 100 milligrams per kilogram of body weight per day.

vii. Chronic feeding tests in dogs at dietary levels of 0.04 percent and 0.2 percent.

viii. Cathartic tests in dogs, using single oral dose.

Tests that were still in progress at the time of the hearing were:

a. FD&C Orange No. 1.

i. Carcinogenicity test in rats, using weekly subcutaneous injections of from 0.25 milliliter to 1.0 milliliter doses of a 2-percent solution.

ii. Chronic feeding tests in dogs at dietary levels of 0.2 percent and 1 percent.

b. FD&C Red No. 32:

i. Chronic feeding test in dogs at a dietary level of 0.01 percent.

Tests of the three colors by external application to determine whether they are toxic when applied externally were being set up at the time of the hearing. (R. 8–78; Ex. 2, 3, 4)

3. The tests that have been concluded are tests normally employed to determine the toxicity of substances taken internally by man. The results of these investigations show that each of the coal-tar colors FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32, taken internally, caused marked damage to various vital organs of the test animals, significant changes in body weight, and premature death.

FD&C Orange No. 1 caused the premature death of all rats on a diet containing 2.0 percent of the test substance. In rats on a diet containing 1.0 percent of this substance there were marked retardation of growth, increased mortality, and chronic congestion and enlargement of the spleen. These same manifestations, to a somewhat lesser extent, were encountered in rats consuming a diet containing 0.5 percent of FD&C Orange No. 1. Dogs consuming 100 milligrams per kilogram per day of FD&C Orange No. 1 died in 26 months to 33 months. They had occasional diarrhea while alive and manifested terminal weight loss. Autopsy revealed congestion and atrophy of the liver attributable to the test substance. On a diet containing 1.0 percent of FD&C Orange No. 1, dogs exhibited chronic diarrhea, rapid deterioration, and weight loss. Autopsy revealed muscular dystrophy and testicular and prostatic atrophy. These same manifestations occurred to a lesser extent in dogs on a diet containing 0.2 percent of FD&C Orange No. 1. A single dose of 100 milligrams to 200 milligrams of FD&C Orange No. 1 produced diarrhea in most dogs. Human volunteers taking 80 milligrams to 100 milligrams in a single dose experienced marked griping and diarrhea.

FD&C Orange No. 2 caused severe growth retardation and increased mortality to rats on a diet containing 0.25 percent of the test substance. At 0.2 percent of the rats' diet there were increased mortality and degeneration of the liver. At a level of 0.1 percent of the substance in the diet, the rats exhibited marked growth retardation. At a level of 0.5 percent, autopsy revealed enlargement of the right side of the heart and slight hypertrophy or hyperplasia of the cells in the liver. Five milligrams per week given to rats by subcutaneous injection caused increased mortality and moderate growth retardation. Dogs consuming 100 milligrams per kilogram of body weight per day of FD&C Orange No. 2 lost weight or gained poorly. Twenty milligrams per kilogram of body weight per day caused one dog in the experiment to gain weight poorly. Dogs on a diet containing 0.2 percent of the test substance had diarrhea at the beginning of the experiment and exhibited rapid deterioration and weight loss. Autopsy revealed atrophy of various vital organs caused by the color. At 0.04 percent of the diet, dogs gradually deteriorated and lost weight, and autopsy revealed atrophy of various vital organs. A single dose of 200 milligrams produced diarrhea in dogs.

When FD&C Red No. 32 was fed to rats at a level of 2.0 percent of the diet, all the rats died within a week. At a 1.0-percent level, death occurred within 12 days. At 0.5 percent most of the rats died within 26 days. At 0.25 percent approximately half of the rats died within 3 months. All the rats showed marked growth retardation and anemia. Autopsy revealed moderate to marked liver damage. Similar but less severe results

[1] The citations following each finding of fact refer to the pages of the transcript of the testimony and the exhibits received in evidence at the hearing, except for citations to the FEDERAL REGISTER, where applicable.

were obtained with rats on a diet containing 0.1 percent of FD&C Red No. 32. In addition to liver damage, however, autopsy also revealed enlargement of the right side of the heart in this latter group. Subcutaneous injection of approximately 10 milligrams per week caused death within 8 weeks to most rats on the experiment. These rats exhibited anemia, hemorrhage, and reduction in the size of the liver. Dogs taking 100 milligrams per kilogram of body weight per day showed moderate weight loss. A level of 0.2 percent of FD&C Red No. 32 in the diet of dogs caused rapid deterioration and weight loss and sporadic diarrhea; 0.04 percent caused gradual deterioration and weight loss, sporadic diarrhea, moderate atrophy of vital organs, and muscular dystrophy. 0.01 percent in the diet caused weight loss and the death of one out of four dogs. A single oral dose of 100 milligrams or 200 milligrams gave diarrhea in the majority of the dogs tested.

The results of pharmacological tests, conducted by qualified investigators using recognized scientific methods, establish that the colors are not harmless substances, but on the contrary are definitely toxic and exert pronounced physiological effects on body tissue. The experimental work on man is limited, and except for Orange 1, adverse effects on man have not been definitely confirmed. (R. 8–87, Ex. 2, 3, 4)

4. The coal-tar colors listed in the regulations as FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32 may be used at present in externally applied drugs and cosmetics as well as products for internal consumption. Tests designed to examine the toxicity of these colors, when used externally, are not complete. (R. 46–48, 63–65)

5. Modification of 21 CFR 135.11 (d) (2) to eliminate the requirement for 3 months' written notice of change in composition of a coal-tar color mixture will facilitate the marketing of substitute mixtures and reduce confusion that may result from the deletion of a straight color from the listings at 21 CFR 135.3, 135.4, and 135.5. (R. 88, 89)

Conclusions. 1. Based upon the evidence of toxicity presented at the hearing, the coal-tar colors FD&C Orange No. 1 (monosodium salt of 4-*p*-sulfophenylazo-1-naphthol), FD&C Orange No. 2 (1-*o*-tolylazo-2-naphthol) and FD&C Red No. 32 (1-xylylazo-2-naphthol) described in the coal-tar color regulations, 21 CFR 135.3, are not harmless and suitable for use within the meaning of sections 406 (b) 504, and 604 of the Federal Food, Drug, and Cosmetic Act (21 U. S. C. 346 (b), 354, and 364) in coloring food or for use in coloring drugs or cosmetics intended for other than external application.

2. The coal-tar colors FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32 should be deleted from the listing at 21 CFR 135.3, since the Secretary cannot continue to list these colors as colors that the Food and Drug Administration will certify as harmless and suitable for use in coloring food or in coloring drugs and cosmetics intended for other than external application.

3. Colors conforming to the present regulations and specifications for FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32 should be added to the listing at 21 CFR 135.5, for use in coloring externally applied drugs and cosmetics only.

4. The provisions of 21 CFR 135.11 (d) (2) requiring 3 months' written notice of a change in the composition of a coal-tar color mixture should be waived when such change is made necessary by deletion of one or more straight colors from the listings at 21 CFR 135.3, 135.4, or 135.5.

Therefore, it is proposed that Part 135—Color Certification be amended in the following respects:

1. In § 135.3 (a) delete the colors FD&C Orange No. 1, FD&C Orange No. 2, and FD&C Red No. 32.

2. Add the following to § 135.5 (a)

EXT D&C ORANGE No. 3

SPECIFICATIONS

Monosodium salt of 4-*p*-sulfophenylazo-1-naphthol.

Volatile matter (at 135° C.), not more than 10.0 percent.

Water-insoluble matter, not more than 0.3 percent.

Ether extracts, not more than 0.2 percent.

α-Naphthol, not more than 0.1 percent.

Chlorides and sulfates of sodium, not more than 4.0 percent.

Mixed oxides, not more than 1.0 percent.

Orange II, not more than 5.0 percent.

Pure dye (as determined by titration with titanium trichloride), not less than 85.0 percent.

EXT D&C ORANGE No. 4

SPECIFICATIONS

1-*o*-Tolylazo-2-naphthol.

Volatile matter (at 100° C.), not more than 0.5 percent.

Sulfated ash, not more than 0.3 percent.

Water-soluble matter, not more than 0.3 percent.

Matter insoluble in carbon tetrachloride, not more than 0.5 percent.

o-Toluidine, not more than 0.05 percent.

β-Naphthol, not more than 0.05 percent.

Pure dye (as determined by titration with titanium trichloride), not less than 98.0 percent.

Melting point, not less than 123.0° C.

EXT D&C RED No. 14

SPECIFICATIONS

1-Xylylazo-2-naphthol.

Volatile matter (at 100° C.), not more than 0.5 percent.

Sulfated ash, not more than 0.3 percent.

Water-soluble matter, not more than 0.3 percent.

Matter insoluble in carbon tetrachloride, not more than 0.5 percent.

Xylidene, not more than 0.1 percent.

β-Naphthol, not more than 0.05 percent.

m-Xylidine in xylidine obtained by reduction of the dye, not more than 30.0 percent.

Pure dye (as determined by titration with titanium trichloride), not less than 97.0 percent.

Boiling range of xylidine, obtained by reduction of the dye, 95 percent between 212°–232° C.

3. Amend § 135.11 (d) (2) so that, as amended, it will read as follows:

§ 135.11 *Labeling.* * * *

(d) * * *

(2) The name of such mixture is the same as or simulates the name of a previously certified batch of a mixture containing a different substance, or a different percentage of a pure dye; but this provision shall not apply if:

(i) The person who requests certification of such batch is the owner of such name and has given 3 months' written notice to the Food and Drug Administration specifying the change to be made in the composition of such mixture; or

(ii) Such change results from removal of a color from the listings in §§ 135.3, 135.4, and 135.5.

Any interested person whose appearance was filed at the hearing may, within 30 days from the date of the publication of this tentative order in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, Health, Education, and Welfare Building, 330 Independence Avenue SW., Washington, D. C., written exceptions thereto. Exceptions shall point out with particularity the alleged errors in this tentative order and shall contain specific references to the pages of the transcript of the testimony or to the exhibits on which such exceptions are based. Such exceptions may be accompanied by a memorandum or brief in support thereof. Exceptions and accompanying memoranda or briefs shall be submitted in quintuplicate.

Dated: December 22, 1954.

[SEAL] NELSON A. ROCKEFELLER,
Acting Secretary.

[F. R. Doc. 54-10346; Filed, Dec. 29, 1954; 8:49 a. m.]