The revisions and addition read as follows:

§ 220.46 Medical evidence.

(a) *Acceptable medical sources.* The Board needs reports about the claimant's impairment(s) from acceptable medical sources. Acceptable medical sources are—

(1) Licensed physicians (medical or osteopathic doctors);

(2) Licensed or certified psychologists at the independent practice level;

(3) Licensed or certified school psychologists, or other licensed or certified individuals with another title who perform the same function as a school psychologist in a school setting (for impairments of intellectual disability, learning disabilities, and borderline intellectual functioning only);

(4) Licensed optometrists (for impairments of visual disorders, or for the measurement of visual acuity and visual fields only, depending on the scope of practice in the State in which the optometrist practices);

(5) Licensed podiatrists (for impairments of the foot only, or foot and ankle only, depending on the scope of practice in the State in which the podiatrist practices);

(6) Qualified speech-language pathologists (for speech or language impairments only.) For this source, *qualified* means that the speech-language pathologist must be licensed by the State professional licensing agency, or be fully certified by the State education agency in the State in which the speech-language pathologist practices, or hold a Certificate of Clinical Competence in Speech-Language Pathology from the American Speech-Language-Hearing Association;

(7) Licensed audiologists (for impairments of hearing loss, auditory processing disorders, and balance disorders within the licensed scope of practice only);

(8) Licensed Advanced Practice Registered Nurses or other licensed advance practice nurses with another title (for impairments within the individual's licensed scope of practice only);

(9) Licensed Physician Assistants/Physician Associates (for impairments within the individual's licensed scope of practice); or

(10) Persons authorized to furnish a copy or summary of the records of a medical facility. Generally, the copy or summary should be certified as accurate by the custodian or by any authorized employee of the Railroad Retirement Board, Social Security Administration, Department of Veterans Affairs, or State agency.

(b) *Other medical sources.* Individuals who are licensed as healthcare workers by a State and are working within the scope of practice permitted under State or Federal law, other than acceptable medical sources identified in paragraph (a) of this section, are other medical sources. Examples include licensed clinical social workers, naturopaths, and chiropractors. The Board will accept and consider evidence from other medical sources about the claimant's impairment(s) and the effect on the claimant's ability to work, but the presence of a medically determinable physical or mental impairment must be established with objective medical evidence from an acceptable medical source as defined in paragraph (a) of this section.

(c) * * *

(6) * * *

(i) Statements about what the claimant can still do despite his or her impairment(s) based on the medical source's findings on factors in paragraphs (c)(1) through (5) of this section (except in disability claims for remarried widow's and surviving divorced spouses). (See § 220.112).

(ii) Statements about what the claimant can still do (based on the medical source's findings on factors in paragraphs (c)(1) through (5) of this section) should describe—

* * * * *

(d) *Completeness.* The medical evidence, including the clinical and laboratory findings, must be complete and detailed enough for the Board to determine whether the claimant is disabled. Specifically, it must allow the Board to determine—

* * * * *

(e) *Evidence from treating medical sources.* A statement by or the opinion of the claimant's treating medical source will not determine whether the claimant is disabled. However, the medical evidence provided by a treating medical source will be considered by the Board in making a disability decision. A treating medical source is a medical source to whom the claimant has been going for treatment on a continuing basis. The claimant may have more than one treating medical source. The Board may use consulting physicians or other medical consultants for specialized examinations or tests, to obtain more complete evidence, and to resolve any conflicts. A consulting physician is a doctor (often a specialist) to whom the claimant is referred for an examination once or on a limited basis. (See § 220.50 for an explanation of when the Board may request a consultative examination.)

(f) *Information from non-medical sources.* Information from other sources may also help the Board understand how an impairment affects the claimant's ability to work. Other sources include—

(1) Public and private social welfare agency personnel;

(2) Family members, caregivers, friends, and neighbors of the claimant;

(3) Educational personnel such as teachers, counselors, and daycare center workers;

(4) Railroad and nonrailroad employers; and,

(5) The claimants themselves.

Dated: January 7, 2025.

By Authority of the Board.

Stephanie Hillyard,

Secretary to the Board.

[FR Doc. 2025–00515 Filed 1–15–25; 8:45 am]

BILLING CODE 7905–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 74

[Docket No. FDA–2023–N–0437]

Color Additive Petition From Center for Science in the Public Interest, et al.; Request To Revoke Color Additive Listing for Use of FD&C Red No. 3 in Food and Ingested Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; order.

SUMMARY: The Food and Drug Administration (FDA or we) is granting a color additive petition submitted by Center for Science in the Public Interest, et al., by repealing the color additive regulations that permit the use of FD&C Red No. 3 in foods (including dietary supplements) and in ingested drugs. The petitioners provided data demonstrating that this additive induces cancer in male rats. Therefore, FDA is revoking the authorized uses in food and ingested drugs of FD&C Red No. 3 in the color additive regulations.

DATES: This order is effective January 15, 2027, except for amendatory instruction 4, which is effective January 18, 2028. If any provisions are delayed or stayed by the filing of proper objections, FDA will publish such notification in the **Federal Register**. Submit either electronic or written objections and requests for a hearing on the order by February 18, 2025. See

section X for further information on the filing of objections.

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of February 18, 2025. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic objections in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on *https://www.regulations.gov.*
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper objections submitted to the Dockets Management Staff, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2023–N–0437 for ''Color Additive Petition from Center for Science in the Public Interest, et al.; Request to Revoke Color Additive Listing for Use of FD&C Red No. 3 in Food and Ingested Drugs.'' Received objections, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of objections. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your objections and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Shayla West-Barnette, Office of Premarket Additive Safety, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–1262; or Alexandra Beliveau, Office of Policy, Regulations, and Information, Human Foods Program, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–2378.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In the **Federal Register** of February 17, 2023 (88 FR 10245), we announced that we filed a color additive petition (CAP 3C0323) jointly submitted by the Center for Science in the Public Interest, Breast Cancer Prevention Partners, Center for Environmental Health, Center for Food Safety, Chef Ann Foundation, Children's Advocacy Institute, Consumer Federation of America, Consumer Reports, Defend Our Health, Environmental Defense Fund, Environmental Working Group, Feingold Association of the United States, Food & Water Watch, Healthy Babies Bright Futures, Life Time Foundation, Momsrising, Prevention Institute, Public Citizen, Public Health Institute, Public Interest Research Group, Real Food for Kids, Lisa Y. Lefferts, Linda S. Birnbaum, and Philip J. Landrigan, c/o Mr. Jensen Jose, 1250 I Street NW, Ste 500, Washington, DC 20005 (the petitioners).

The petition proposed that we repeal the color additive regulations for FD&C Red No. 3 in § 74.303 (21 CFR 74.303), which permits the use of FD&C Red No. 3 in foods (including dietary supplements), and § 74.1303 (21 CFR 74.1303), which permits the use of FD&C Red No. 3 in ingested drugs. The notice of petition gave interested parties until April 18, 2023, to submit comments on the filed color additive petition. In response to a written request submitted to the docket, we extended the comment period to May 18, 2023 (88 FR 19026, March 30, 2023). This order granting the request to revise the regulations to no longer provide for these uses of FD&C Red No. 3 responds to the petition.

II. Background

A. Statutory and Regulatory Background of Color Additive Regulation

The Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes us to regulate ''color additives'' (see section 721(b) of

the FD&C Act (21 U.S.C. 379e(b))). The FD&C Act defines ''color additive'' as ''a material which . . . is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and . . . [that] when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with [an]other substance) of imparting color thereto . . . The term ''color'' includes black, white, and intermediate grays . . .'' (see section 201(t) of the FD&C Act (21 U.S.C. 321(t))). Color additives used in or on a food, drug, cosmetic, or certain medical devices are deemed unsafe and prohibited except to the extent that we approve their use (see section 721(a) of the FD&C Act). Certain color additives must be certified by FDA (see section 721(c) of the FD&C Act).

The FD&C Act provides a process through which any person who wishes to use a color additive in or on food, drugs, certain devices, or cosmetics, may submit a petition proposing the issuance of a color additive regulation listing such use with supporting information. A color additive petition may also be submitted to propose the amendment or repeal of any existing color additive regulation (see section 721(b)(5)(C) and (d) of the FD&C Act). In response to a color additive petition, FDA may issue a regulation listing a color additive for use in or on food, drugs, devices, or cosmetics only if it determines that the additive is suitable and safe for such use (see section 721(b)(2)(A) of the FD&C Act). FDA's determination that a color additive is safe means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended condition of use of the color additive (21 CFR 70.3(i)), which we refer to as ''a reasonable certainty of no harm.'' This safety standard is referred to as the ''general safety clause'' for color additives. To determine whether a color additive is safe under the general safety clause, the FD&C Act requires FDA to consider, among other relevant factors: (1) probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs or device, or cosmetics because of the use of the additive; (2) cumulative effect, if any, of such additive ''in the diet of man or animals,'' taking into account the same or any chemically or pharmacologically related substance or substances in such diet; and (3) safety factors recognized by experts ''as appropriate for the use of animal experimentation data'' (see section 721(b)(5)(A) of the FD&C Act).

In addition, section 721(b)(5)(B) of the FD&C Act, often referred to as the Delaney Clause, deems color additives unsafe under certain circumstances. The Delaney Clause consists of two parts. The first part (section 721(b)(5)(B)(i) of the FD&C Act) pertains specifically to ingested color additives. The second part (section 721(b)(5)(B)(ii) of the FD&C Act) applies to noningested color additives. For purposes of our review of this petition, we reviewed these uses of FD&C Red No. 3 under the first part because these uses result in ingestion. Section 721(b)(5)(B)(i) of the FD&C Act states that a color additive shall be deemed unsafe for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal. Courts have concluded that the Delaney Clause completely bans additives found to induce cancer in humans or animals. In *Public Citizen* v. *Young,* 831 F.2d 1108, 1122 (D.C. Cir. 1987), the court held that Congress intended for the Delaney Clause to be ''extraordinarily rigid,'' to protect the public from cancer-causing substances without exception, rejecting FDA's argument that a particular color additive should be approved because it did not pose more than a de minimis cancer risk; see also *Les* v. *Reilly,* 968 F.2d 985, 986 (9th Cir. 1992) (holding that the Environmental Protection Agency's refusal to revoke regulations permitting the use of certain pesticides, which were regulated as food additives at the time of the court decision and subject to a similarly worded Delaney Clause for food additives, on the grounds that they pose a de minimis cancer risk, is contrary to the provisions of the Delaney Clause).

There is a similar Delaney Clause provision for food additives under section 409(c)(3) of the FD&C Act (21 U.S.C. 348(c)(3)), which states that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. In revoking certain authorizations for food additives under the Delaney Clause, FDA stated that the Delaney Clause limits FDA's discretion to determine the safety of food additives. FDA stated that the Delaney Clause prevents FDA from finding a food additive to be safe if it has been found to induce cancer when ingested by humans or animals, ''regardless of the probability, or risk, of cancer associated with exposure to the additive or of the extent to which the experimental conditions of the animal study or the carcinogenic mode of action provide insight into the health effects of human consumption and use of the additive in question'' (83 FR 50490 at 50492, October 9, 2018).

Section 721(d) of the FD&C Act provides for the issuance, amendment, or repeal of regulations authorizing the use of a color additive, and, among other things, it specifies that the safety provisions of section 721(b)(5) apply to such actions. For FDA to grant a petition that seeks repeal of a color additive regulation based upon new data concerning the safety of the color additive, such data must be adequate for FDA to conclude that there is no longer a reasonable certainty of no harm for the intended use of the color additive or that it must be deemed unsafe under the Delaney Clause.

B. Chemical Identity and Nomenclature of FD&C Red No. 3

Our regulation, at § 74.303, describes FD&C Red No. 3 as principally the monohydrate of 9 (*o*-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, with smaller amounts of lower iodinated fluoresceins. The color is also called erythrosine or other names, including Colour Index (C.I.) Acid Red 51; C.I. No. 45430; and C.I. Food Red 14. FD&C Red No. 3 is required to be certified by FDA that it complies with §§ 74.303 and 74.1303. The designation ''FD&C Red No. 3'' is permitted only for those batches of the color additive that have been certified by FDA.

C. History of FDA's Regulatory Actions for FD&C Red No. 3

FD&C Red No. 3, as erythrosine, was first listed in 1907 under the provisions of the Food and Drugs Act of 1906 (Food Inspection Decision 76), and later provisionally listed in 1960 as Red No. 3 for food, drug, and cosmetic use (25 FR 9759, October 12, 1960) (see also Ref. 1). In 1969, FD&C Red No. 3 was permanently listed for use in food and ingested drugs (34 FR 7446, May 8, 1969), now codified in §§ 74.303 and 74.1303. In 1990, FDA did not extend the provisional listing of FD&C Red No. 3 for use in cosmetics and externally applied drugs (55 FR 3516, February 1, 1990) based on thyroid neoplasia in rat carcinogenicity studies, which terminated this listing. The decision did not revoke the existing permanent listing for food and ingested drugs from 1969.

III. Summary and Context of Determination

We have evaluated the data and information submitted in the petition as well as other relevant data. FDA finds that FD&C Red No. 3 can induce cancer in male rats, through a rat specific hormonal mechanism. Therefore, we are revoking the listings providing for these uses of this color additive under section 721(b)(5)(B) of the FD&C Act as a matter of law, as described further below.

IV. Evaluation of Petition

The petitioners state that FD&C Red No. 3 has been shown to induce cancer in male laboratory rats. The petitioners discuss multiple regulatory conclusions that FD&C Red No. 3 is carcinogenic in male rats, which are based on some in vivo studies. Specifically, data reported in the publication entitled ''Lifetime Toxicity/Carcinogenicity Study of FD&C Red No. 3 (erythrosine) in Rats'' by Borzelleca et al., a compilation of two separate chronic toxicity and carcinogenicity studies, was published in 1987. These conclusions include a 1990 conclusion from FDA (55 FR 3520, February 1, 1990); a 1983 National Toxicology Program (NTP) subcommittee conclusion; a 1989 European Commission's Scientific Committee for Food report (Ref. 2); and Joint Food and Agricultural Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) conclusions (Refs. 3 and 4).

FDA evaluated the data cited by the petitioner, as well as other available data. Based on our review of this data and information, we conclude that the Delaney Clause applies because FD&C Red No. 3 has been found to ''induce cancer when ingested by . . . animal.'' Specifically, some in vivo studies have shown FD&C Red No. 3 can induce thyroid tumors in male rats. Thyroid tumors in male rats appear to result from perturbation in the hypothalamic-pituitary-thyroid hormonal axis (Refs. 5 and 6). These perturbations are initiated by an increase in circulating thyroid stimulating hormone (TSH), causing follicular hyperplasia, which has the potential to develop into thyroid tumors (Refs. 5 and 6). Thus, increased TSH levels appears to be a key event for thyroid tumor development from FD&C Red No. 3 exposure in male rats (Refs. 5 and 6).

Based on the available data and information, FD&C Red No. 3-induced thyroid tumors in male rats are of limited relevance to humans. FDA's Center for Food Safety and Applied Nutrition (CFSAN)'s Cancer Assessment Committee (CAC) concluded that while studies show FD&C Red No. 3 induces thyroid tumors in male rats, the risk of developing such tumors in humans at low exposure levels from the current uses is unlikely (Ref. 5). FD&C Red No. 3 is likely not genotoxic (in other words, it is not directly DNA reactive) (Refs. 5 and 6). FD&C Red No. 3 appears to induce thyroid tumors in male rats through a key event—an increase in circulating TSH—and rodents show much higher sensitivity to such perturbations compared to humans (Refs. 5 and 6). There is no conclusive available clinical evidence that demonstrates increased TSH levels either promote or actively cause thyroid carcinogenesis in humans (Refs. 5 and 6). Further, studies in humans to date have failed to show convincing evidence that FD&C Red No. 3 exposure results in consistent perturbations in any thyroid hormone levels, including TSH (Refs. 5 and 6). FDA estimated the highest exposure for FD&C Red No. 3 from the approved uses as a color additive in conventional food, dietary supplements, and ingested drugs to be 0.25 milligrams per kilogram of bodyweight per day (mg/kg bw/day) (Ref. 7). When compared against the No Observed Adverse Effect Level for thyroid hormone effects associated with thyroid tumors in male rats of 35.8 mg/kg bw/day, a 210-fold margin of exposure was derived (Ref. 5). Based on the available data and information, FDA and other regulatory agencies including JECFA, the European Food Safety Authority (EFSA), and the Food Standards Australia New Zealand (FSANZ) have concluded that FD&C Red No. 3-induced thyroid tumors in rats are of limited relevance to humans (Refs. 5 and 6). In addition, the carcinogenicity of FD&C Red No. 3 was not observed when tested in other animals including female rats and either sex of mice, gerbils, or dogs (Refs. 5 and 6).

Despite its limited relevance to humans, the cumulative data and information show that high exposure to FD&C Red No. 3 induces thyroid tumors in male rats (Refs. 5 and 6).

V. Comments on the Notice of Petition

FDA received a number of comments in response to the notice of filing of the petition. Most comments expressed general support for revocation of the regulations for FD&C Red No. 3, without providing any additional information.

We summarize and respond to relevant portions of comments in this order. To make it easier to identify comments and FDA's responses to the comments, the word ''Comment'' will appear in parenthesis before the description of the comment, and the word ''Response'' will appear in parentheses before FDA's response. We have also numbered each comment to help distinguish between different comments. The number assigned to each comment is for organizational purposes only and does not signify the comment's value, importance, or the order in which it was submitted.

(Comment 1) Several comments argued that the Delaney Clause does not apply because the scientific community's understanding of the carcinogenicity potential of FD&C Red No. 3 has evolved since inclusion of the Delaney Clause in the FD&C Act and since FDA's conclusion (55 FR 3520) that FD&C Red No. 3 induces cancer in male rats. Some comments argue that FDA has discretion to exercise scientific judgment in determining whether FD&C Red No. 3 induces cancer for purposes of the Delaney Clause.

(Response 1) We agree that a large body of literature has been published since FDA's conclusion that FD&C Red No. 3 induces cancer in male rats. We have reviewed the currently available data and information pertaining to the safety of FD&C Red No. 3 as a color additive and concluded that the FD&C Red No. 3-induced thyroid tumors in male rats are of limited relevance to humans (Refs. 5 and 6). However, the current literature continues to support the finding that high exposure to FD&C Red No. 3 induces cancer in male rats (Ref. 6). Because of this finding, we disagree that FDA has discretion to determine that FD&C Red No. 3 does not induce cancer under the Delaney Clause. The language of the Delaney Clause is straightforward. Under the general safety clause for color additives, FDA has discretion to review a number of factors to determine whether a color additive is safe (section 721(b)(5)(A) of the FD&C Act). However, for ingested color additives that are shown ''to induce cancer in man or animal,'' the Delaney Clause limits FDA's discretion and requires that FDA conclude that the color additive is not safe as a matter of law.

(Comment 2) Several comments argued that the Delaney Clause does not apply because FD&C Red No. 3 is non-genotoxic and induces tumors through a secondary mechanism. The comments assert that FDA's action to terminate the provisional listing FD&C Red No. 3 in 1990 was because there was inadequate evidence at the time to demonstrate that FD&C Red No. 3 was non-genotoxic, and now that there is evidence demonstrating that FD&C Red No. 3 is non-genotoxic, FDA has discretion to

determine that FD&C Red No. 3 does not cause cancer.

(Response 2) We agree that FD&C Red No. 3 is non-genotoxic based on the available data and information. FD&C Red No. 3 induces tumors in male rats through a key event (increased TSH production) (Ref. 6). We refer to the increase in TSH levels as a ''key event'' and not as a secondary mechanism because the exact mechanism of FD&C Red No. 3-induced carcinogenesis in male rats has not been determined. Nonetheless, we disagree with the comments' assertion that the Delaney Clause does not apply. As we concluded in our 2018 action revoking the authorizations of certain food additives under a similarly worded Delaney Clause, the Delaney Clause does not differentiate between non-genotoxic and genotoxic carcinogens (83 FR 50490 at 50501). Nor does the Delaney Clause permit FDA to find an ingested color additive safe for human consumption if the color additive has been found to induce cancer in animals. Consistent with our conclusion in revoking certain food additive approvals based on the Delaney Clause (83 FR 50490), FDA concludes that the Delaney Clause limits FDA's discretion to determine the safety of color additives that are intended to be ingested (such as the use of FD&C Red No. 3 in food and ingested drugs) in that it prevents FDA from finding such a color additive to be safe if it has been found to induce cancer when ingested by humans or animals, regardless of the probability, or risk, of cancer associated with exposure to the additive or of the extent to which the experimental conditions of the animal study or the carcinogenic mode of action provide insight into the health effects of human consumption and use of the additive in question.

(Comment 3) One comment argued that the evidence demonstrating that FD&C Red No. 3 induces thyroid tumors in male rats is insufficient to invoke the Delaney Clause.

(Response 3) We disagree. Again, we acknowledge the large body of published literature that does not show FD&C Red No. 3 inducing cancer in female rats, or multiple other animal species, including humans (Refs. 5 and 6). However, under the Delaney Clause, these negative findings do not outweigh or negate the positive findings of the two chronic feeding studies. Because FD&C Red No. 3 has been found to induce tumors in male rats, FDA must revoke the regulations providing for these uses of the color additive as a matter of law.

(Comment 4) One comment argued that the Delaney Clause does not apply because the dose range used for the two chronic feeding studies in rats render the positive findings unreliable. Specifically, the comment asserts that in its 1990 order, the study FDA relied on was unreliable because the dose of FD&C Red No. 3 exceeded the maximum tolerated dose. The comment asserts that this violates the testing guidelines of the National Cancer Institute.

(Response 4) We disagree. The two chronic feeding studies in rats were appropriately designed and considered to be positive bioassays (Ref. 5). These two studies reported within a single manuscript were considered appropriate and not to have exceeded the maximum tolerated dose (MTD) per current guidance (Redbook 2000, Chapters II.C.5.A. and IV.C.7. or IV.C.8) (Ref. 5). Redbook 2000 uses the NTP's definition of MTD, which states that the MTD is ''that dose which, when given for the duration of the chronic study as the highest dose, will not shorten the treated animals' longevity from any toxic effects other than the induction of neoplasms.'' The data that was deemed to demonstrate FD&C Red No. 3 is carcinogenic in male rats used a maximum dose of 4 percent (Borzelleca et al., 1987), which did not impact the longevity of the treated animals' life spans, resulted in no systemic toxic effects other than the induction of neoplasms, and did not cause unacceptable side effects. Thus, the dose scheme used by Borzelleca et al. (1987) fits the FDA Redbook 2000 definition of MTD. Furthermore, while rats may not be an ideal model to assess the carcinogenicity potential of FD&C Red No. 3 in humans, these chronic feeding studies do reasonably demonstrate that FD&C Red No. 3 induces thyroid tumors in male rats. These studies are sufficient to invoke the Delaney Clause because the Delaney Clause is not limited to inducing cancer in humans.

(Comment 5) One comment requested that FDA convene a Color Additive Advisory Committee if FDA delists FD&C Red No. 3 on the basis of the Delaney Clause.

(Response 5) We decline to convene the meeting requested by the comment. Section 721(b)(5)(c)(i) of the FD&C Act states that any person who will be adversely affected by a proposal if placed into effect may request, within the specified time period, that the petition or order be referred to an advisory committee for a report and recommendations with respect to any matter arising under subparagraph (B) (here, the Delaney clause, (B)(i)) that is involved in the proposal) and that requires the exercise of scientific judgment. Upon such request, the Secretary must appoint an advisory committee. FDA's determination that FD&C Red No. 3 has been shown to cause cancer in laboratory animals is based on a comprehensive review of all relevant carcinogenicity studies (Ref. 6). After reviewing these studies, FDA did not find there to be a genuine debate regarding the science—specifically, that FD&C Red No. 3 induced cancer in male rats. Thus, FDA's conclusion that FD&C Red No. 3 has been shown to cause cancer in laboratory animals is not a matter that requires referral to an advisory committee because it did not require the exercise of scientific judgment.

(Comment 6) A couple of comments stated that the highest dietary exposure to FD&C Red No. 3 is below the Acceptable Daily Intake (ADI) and therefore, dietary exposure from its use as a food color additive does not present a safety concern. Another comment stated that because of the relatively low dietary exposure to FD&C Red No. 3, revoking the regulations authorizing its use would not significantly reduce risk to the public.

(Response 6) Based on our evaluation of the dietary exposure to FD&C Red No. 3 and the available scientific evidence, we conclude that FD&C Red No. 3 meets the safety standard of a reasonable certainty of no harm required for a color additive (see Refs. 6 and 7). We derived a 210-fold margin of exposure between the highest dietary exposure to FD&C Red No. 3 (0.25 mg/kg bw/d) and the No Observed Adverse Effect Level chosen by the CAC (35.8 mg/kg bw/d) (Ref. 6). We agree that the highest dietary exposure to FD&C Red No. 3 is below the ADI established by JECFA in 2018 (6 mg/kg bw/d). We also agree with JECFA's conclusion that the possibility of developing thyroid tumors in humans at low dietary exposure levels from the current uses of FD&C Red No. 3 is unlikely (Ref. 6). However, as a matter of law (see section 721(b)(5)(B) of the FD&C Act), we must revoke the regulations authorizing the uses of FD&C Red No. 3 because it has been shown to induce cancer in male rats.

(Comment 7) Several comments stated that the findings that FD&C Red No. 3 induces cancer in male rats are not applicable to humans and, therefore, do not indicate that the color additive would induce tumors in humans. These comments asserted that the conclusions of other regulatory agencies and authoritative risk assessment bodies support that the use of FD&C Red No. 3 is unlikely to cause tumors in humans.

(Response 7) We agree that there are physiological differences between rats

and humans that require contextualization when extrapolating the relevance of animal studies to humans. There is no conclusive evidence that increased TSH production—a key event for tumor induction in male rats—causes thyroid carcinogenesis in humans (see Ref. 6). Furthermore, studies in humans have not demonstrated that dietary exposure to FD&C Red No. 3 causes consistent perturbations of TSH or other hormones. In fact, studies in humans demonstrate a lack of effects on the thyroid. Based on the scientific evidence, we agree that the thyroid tumors observed in male rats are of limited relevance to humans, and we note that JECFA, EFSA, and the FSANZ have also reached this same conclusion (Ref. 6). However, as stated earlier, we must revoke the regulations authorizing the uses of FD&C Red No. 3 because it has been shown to induce cancer in male rats (see section 721(b)(5)(B) of the FD&C Act). The Delaney Clause prevents us from finding its use to be safe, regardless of the extent to which the experimental conditions of the animal study provide insight into the health effects of human consumption and use of the color additive in question.

(Comment 8) One comment asserts that FDA is required to consider reasonable alternatives to revoking the color additive listings for FD&C Red No. 3. The comment also asserts that the ''proposed rule does not indicate whether FDA investigated this issue of reasonably viable alternatives to FD&C Red. 3.''

(Response 8) Under section 721(b) of the FD&C Act, a color additive may not be marketed unless FDA determines that the additive is suitable and safe for such use. Under section 721(b)(5)(B) of the FD&C Act, also referred to as the Delaney Clause, a color additive shall be deemed unsafe, and shall not be listed, if certain conditions are met. As FDA has determined that the Delaney Clause applies to the authorized uses of FD&C Red No. 3, FDA does not have discretion to consider alternatives to revoking the color additive listing, and that is true regardless of whether there are ''reasonably viable alternatives'' for this color additive.

(Comment 9) One comment asserts that FDA did not disclose the relevant studies in the filing notice.

(Response 9) We disagree. As required under section 721(d)(1), FDA is required to publish ''notice of the proposal made by the petition . . . in general terms.'' Furthermore, we note that the petition, which was included in the public docket, included citations to the relevant studies.

VI. Conclusion

Upon review of the available information, we have determined that the information provided in the petition and other publicly available relevant data demonstrate that FD&C Red No. 3 has been shown to cause cancer in laboratory animals. Under the Delaney Clause this finding of carcinogenicity renders the color additive ''unsafe'' as a matter of law. FDA is revoking the authorizations for this substance as a color additive to no longer provide for the use of FD&C Red No. 3 in food and ingested drugs. Therefore, we are amending 21 CFR part 74 as set forth in this document. We consider this action to also partially respond to CSPI's 2008 citizen petition (Docket No. FDA–2008–P–0349).

Because the effective date for the removal of § 74.303 will occur before the effective date for the removal of § 74.1303, we are also amending § 74.1303 to add the identity and specifications from § 74.303(a)(1) and (b), which are currently referenced in § 74.1303(a). This amendment will become effective on the effective date for the removal of § 74.303.

Upon the removal of these color additive listings, FDA will no longer provide certificates for FD&C Red No. 3. In accordance with 21 CFR 80.32(h), all certificates for existing batches and portions of batches of FD&C Red No. 3 will cease to be effective for use in food on the effective date for the removal of § 74.303 and for use in ingested drugs on the effective date for the removal of § 74.1303, and any lots of FD&C Red No. 3 will be regarded as uncertified after the relevant date(s). Use of FD&C Red No. 3 after its certificate ceases to be effective will result in such food or ingested drugs being adulterated. When FD&C Red No. 3 has been used in food or ingested drugs while its certificate is still effective, such food or ingested drugs will not be regarded as adulterated by reason of the use of such color additive.

VII. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see **FOR FURTHER INFORMATION CONTACT**). As provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

VIII. Analysis of Environmental Impacts

We have determined under 21 CFR 25.32(m) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This order contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Objections

This order is effective as shown in the **DATES** section, except as to any provisions that may be stayed by the filing of proper objections under sections 701(e)(2) and 721(d) of the FD&C Act (21 U.S.C. 371(e)(2) and 379e(d)). If you will be adversely affected by one or more provisions of this regulation, you may file with the Dockets Management Staff (see **ADDRESSES**) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *https://www.regulations.gov.* We will publish notice of the objections that we have received or lack thereof in the **Federal Register**.

XI. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public

display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

* 1. Memorandum from S. West-Barnette, Division of Food Ingredients, Regulatory Review Branch, to M. Honigfort, Division of Food Ingredients, Regulatory Review Branch, June 6, 2024.
2. SCF. Reports of the Scientific Committee for Food (21st series), 1989. Available at: *http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_21.pdf* (accessed January 16, 2024).
3. JECFA, Evaluation of Certain Food Additives and Contaminants: Thirty-seventh Report, 1991. Available at: *https://www.who.int/publications/i/item/9241208066* (accessed January 16, 2024).
4. JECFA, Safety Evaluation of Certain Food Additives: Eighty-sixth Report, 2020. Available at: *https://www.who.int/publications/i/item/9789240004580* (accessed January 16, 2024).
* 5. CFSAN CAC Full Committee Review, Memorandum of Meeting, October 15, 2019.
* 6. Memorandum from J. Gingrich, Division of Food Ingredients, Toxicology Review Branch, to S. West-Barnette, Division of Food Ingredients, Regulatory Review Branch, June 18, 2024.
* 7. Memorandum from D. Doell, Chemistry Review Group, Division of Petition Review (DPR), Office of Food Additive Safety (OFAS), CFSAN, FDA, to J. Kidwell, Regulatory Review Group I, DPR, OFAS, CFSAN, FDA, September 18, 2015.

List of Subjects in 21 CFR Part 74

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 74 is amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

■ 1. The authority citation for part 74 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

§ 74.303 [Removed]

■ 2. Remove § 74.303.

■ 3. Revise § 74.1303 to read as follows:

§ 74.1303 FD&C Red No. 3.

(a) *Identity.* (1) The color additive FD&C Red No. 3 is principally the monohydrate of 9 (*o*-carboxyphenyl)-6-hydroxy-2,4,5,7-tetraiodo-3H-xanthen-3-one, disodium salt, with smaller amounts of lower iodinated fluoresceins.

(2) Color additive mixtures for ingested drug used made with FD&C Red No. 3 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 ingested drugs.

(b) *Specifications.* FD&C Red No. 3 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by good manufacturing practice:

(1) Volatile matter (at 135 °C) and chlorides and sulfates (calculated as the sodium salts), total not more than 13 percent.

(2) Water-insoluble matter, not more than 0.2 percent.

(3) Unhalogenated intermediates, total not more than 0.1 percent.

(4) Sodium iodide, not more than 0.4 percent.

(5) Triiodoresorcinol, not more than 0.2 percent.

(6) 2(2′,4′-Dihydroxy-3′, 5′-diiodobenzoyl) benzoic acid, not more than 0.2 percent.

(7) Monoiodofluoresceins not more than 1.0 percent.

(8) Other lower iodinated fluoresceins, not more than 9.0 percent.

(9) Lead (as Pb), not more than 10 parts per million.

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

(11) Total color, not less than 87.0 percent.

(c) *Uses and restrictions.* FD&C Red No. 3 may be safely used for coloring ingested drugs in amounts consistent with 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 FD&C Red No. 3 shall be certified in accordance with regulations in part 80 of this chapter.

§ 74.1303 [Removed]

■ 4. Effective January 18, 2028 remove § 74.1303.

Dated: January 10, 2025.

P. Ritu Nalubola,

Associate Commissioner for Policy.

[FR Doc. 2025–00830 Filed 1–15–25; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF THE TREASURY

Alcohol and Tobacco Tax and Trade Bureau

27 CFR Part 16

[Docket No. TTB–2025–0001; Notice No. 236]

Civil Monetary Penalty Inflation Adjustment—Alcoholic Beverage Labeling Act

AGENCY: Alcohol and Tobacco Tax and Trade Bureau, Treasury.

ACTION: Notification of civil monetary penalty adjustment.

SUMMARY: This document informs the public that the maximum penalty for violations of the Alcoholic Beverage Labeling Act (ABLA) is being adjusted in accordance with the Federal Civil Penalties Inflation Adjustment Act of 1990, as amended. Prior to the publication of this document, any person who violated the provisions of the ABLA was subject to a civil penalty of not more than $25,561, with each day constituting a separate offense. This document announces that this maximum penalty is being increased to $26,225.

DATES: The new maximum civil penalty for violations of the ABLA takes effect on January 16, 2025 and applies to penalties that are assessed after that date.

FOR FURTHER INFORMATION CONTACT: Vonzella C. Johnson, Regulations and Rulings Division, Alcohol and Tobacco Tax and Trade Bureau, 1310 G Street NW, Box 12, Washington, DC 20005; (202) 508–0413.

Background

Statutory Authority for Federal Civil Monetary Penalty Inflation Adjustments

The Federal Civil Penalties Inflation Adjustment Act of 1990 (the Inflation Adjustment Act), Public Law 101–410, 104 Stat. 890, 28 U.S.C. 2461 note, as Act of 2015, Public Law 114–74, section 701, 129 Stat. 584, requires the regular adjustment and evaluation of civil monetary penalties to maintain their deterrent effect and helps to ensure that penalty amounts imposed by the Federal Government are properly accounted for and collected. A ''civil monetary penalty'' is defined in the Inflation Adjustment Act as any penalty, fine, or other such sanction that is: (1) For a specific monetary amount as provided by Federal law, or has a maximum amount provided for by Federal law; (2) assessed or enforced by an agency pursuant to Federal law; and