VII. Paperwork Reduction Act of 1995

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

VIII. Objections

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.*

List of Subjects in 21 CFR Part 172

Food additives, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Director, Center for Food Safety and Applied Nutrition, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

■ 1. The authority citation for part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

§ 172.515 [Amended]

■ 2. Amend § 172.515(b) by removing the entry for ''Styrene.''

Dated: October 2, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–21808 Filed 10–5–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 172 and 177

[Docket No. FDA–2015–F–4317]

Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; notification of partial denial of petition.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is partially granting a petition submitted by the Breast Cancer Fund (now known as the Breast Cancer Prevention Partners), Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Consumers Union, Environmental Defense Fund, Environmental Working Group, Improving Kids' Environment, Natural Resources Defense Council, WE ACT for Environmental Justice, and Mr. James Huff, by amending the food additive regulations to no longer authorize the use of benzophenone, ethyl acrylate, eugenyl methyl ether, myrcene, pulegone, and pyridine as synthetic flavoring substances for use in food. We are taking this action because, despite FDA's scientific analysis and determination that these substances do not pose a risk to public health under the conditions of their intended use, the petitioners provided data demonstrating that these additives induce cancer in laboratory animals, and, as a result of this finding in animals, FDA cannot as a matter of law maintain the listing of these synthetic flavoring substances in the food additive regulations. Because of evidence that benzophenone causes cancer in animals, FDA also is amending the food additive regulations to no longer provide for the use of benzophenone as a plasticizer in rubber articles intended for repeated use in contact with food. FDA is denying as moot the portions of the petition proposing that the food additive regulations be amended to no longer authorize the use of styrene as a synthetic flavoring substance because this use has been permanently and completely abandoned. In addition, FDA is declining to act on the petitioners' request to issue a regulation to prohibit the use of these synthetic flavoring substances in food because that issue is not the proper subject of a food additive petition.

DATES: This rule is effective October 9, 2018. See section IX for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing on the final rule by November 8, 2018.

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. Electronic objections must be submitted on or before November 8, 2018. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is 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–2015–F–4317 for ''Food Additives Permitted for Direct Addition to Food for Human Consumption; Synthetic Flavoring Agents and Adjuvants.'' 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.

• 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 comments. 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 comments 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.gpo.gov/fdsys/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.

FOR FURTHER INFORMATION CONTACT: Judith Kidwell, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740–3835, 240–402–1071.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In the **Federal Register** of January 4, 2016 (81 FR 42), we announced that the Center for Science in the Public Interest, Natural Resources Defense Council, Center for Food Safety, Consumers Union, Improving Kids' Environment, Center for Environmental Health, Environmental Working Group, Environmental Defense Fund, and James Huff (the petitioners), c/o Mr. Tom Neltner, 1875 Connecticut Ave. NW, Washington, DC 2009, had jointly filed a food additive petition (FAP 5A4810). Subsequently, the Breast Cancer Fund (now known as Breast Cancer Prevention Partners) and WE ACT for Environmental Justice joined as co-petitioners.

The petition proposed that we take two separate regulatory actions: (1) Amend the food additive regulations in § 172.515 *Synthetic flavoring substances and adjuvants* (21 CFR 172.515) to no longer authorize the use of seven listed synthetic flavoring food additives and (2) to establish zero tolerances in § 172.515 for these additives. However, the food additive regulation is not the appropriate section for a ''zero tolerance,'' and this request is not the proper subject of a food additive petition. A food additive petition must either propose the issuance of a regulation prescribing the conditions under which a food additive may be safely used (see section 409(b)(1) of the Federal Food, Drug, & Cosmetic Act (FD&C Act) (21 U.S.C. 348(b)(1)), or propose the amendment or repeal of an existing food additive regulation (see section 409(i) of the FD&C Act. Only the petitioners' request to amend § 172.515 to remove the seven synthetic flavorings and adjuvants from FDA's regulations permitting their use as additives in food falls within the statutory scope of a food additive petition. Therefore, the petitioners' request that we establish zero tolerances for these seven flavoring additives falls outside the scope of a food additive petition. As a result, we are not addressing that request further in this rule. (An interested person may use the citizen petition process to request the issuance of a regulation, including a request to establish a ''zero tolerance,'' which we interpret as a request to issue a regulation prohibiting a substance from human food under part 189 (see 21 CFR 189.1(c) (referring to 21 CFR part 10, which sets forth FDA's citizen petition process)). (In addition, we understand the petitioners are no longer pursuing this request based on a public filing with a U.S. court of appeals (stating ''[t]he Petition also requested that FDA 'establish a zero tolerance [standard]. . . for the use of these seven flavors.' . . . Petitioners are no longer pursuing this aspect of the Petition''). (See *In Re Breast Cancer Prevention Partners,* No. 18–71260 (9th Cir.)). Thus, in this rule we focus solely on the request to amend the food additive regulations.

The seven food additives that are the subject of this petition are:

1. Benzophenone (also known as diphenylketone) (CAS No. 119–61–9);
2. Ethyl acrylate (CAS No. 140–88–5);
3. Eugenyl methyl ether (also known as 4-allylveratrole or methyl eugenol) (CAS No. 93–15–2);
4. Myrcene (also known as 7-methyl-3-methylene-1,6-octadiene) (CAS No. 123–35–3);
5. Pulegone (also known as *p*-menth-4(8)-en-3-one) (CAS No. 89–82–7);
6. Pyridine (CAS No. 110–86–1); and
7. Styrene (CAS No. 100–42–5).

We stated in the notice of petition that, although the petition only proposes to amend § 172.515 to no longer provide for the use of these seven synthetic flavoring substances, FDA's action in response to the petition could affect other regulations that provide for the use of the additives. Specifically, in the notice we identified the use of benzophenone, which is approved as an indirect food additive, *i.e.,* a plasticizer (diphenylketone in § 177.2600 (21 CFR 177.2600(c)(4)(iv))), as potentially being impacted by our regulatory decision. The notice of petition gave interested parties until March 4, 2016, to submit

comments on the filed food additive petition. In response to a written request submitted to the docket, we extended the comment period to May 3, 2016 (81 FR 8867, February 23, 2016).

This final rule partially granting the request to revise the regulations to no longer provide for the use of these synthetic flavorings in food, and the partial denial given the petitioners' request falls outside the scope of the food additive petition process, completely responds to the petition.

II. Background

A. Statutory and Regulatory Background of Food Additive Regulation

The FD&C Act authorizes us to regulate ''food additives'' (see section 409(a) of the FD&C Act). The FD&C Act defines ''food additive,'' in relevant part, as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food (see section 201(s) of the FD&C Act (21 U.S.C. 321(s))). Food additives can include both substances added directly to food and ''food contact substance[s]'' (*i.e.,* substances intended for use in materials that come into contact with food, for instance in food packaging or manufacturing, but which are not intended to have any technical effect in the food (see § 170.3(e)(3) (21 CFR 170.3(e)(3))). Food additives are deemed unsafe and prohibited except to the extent that we approve their use (see, *e.g.,* section 301(a) and (k) (21 U.S.C. 331(a) and (k)) and 409(a) of the FD&C Act).

The FD&C Act provides a process through which persons who wish to use a food additive may submit a petition proposing the issuance of a regulation prescribing the conditions under which the additive may be safely used (see section 409(b)(1) of the FD&C Act). Such a petition is referred to as a ''food additive petition.'' A food additive petition must either propose the issuance of a regulation prescribing the conditions under which a food additive may be safely used (see section 409(b)(1) of the FD&C Act), or propose the amendment or repeal of an existing food additive regulation (see section 409(i) of the FD&C Act). When we conclude that a proposed use of a food additive is safe, we issue a regulation called a ''food additive regulation'' authorizing a specific use of the substance.

A food additive cannot be approved for use unless the data presented to FDA establish that the food additive is safe for that use (section 409(c)(3)(A) of the FD&C Act). To determine whether a food additive is safe, the FD&C Act requires FDA to consider, among other relevant factors: (1) Probable consumption of the additive; (2) cumulative effect of such additive ''in the diet of man or animals''; and (3) safety factors recognized by experts ''as appropriate for the use of animal experimentation data'' (section 409(c)(5) of the FD&C Act). FDA's determination that a food additive use is safe means that there is a ''reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use'' (§ 170.3(i)). However, FDA cannot approve a food additive if it is found ''to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal'' (section 409(c)(3)(A) of the FD&C Act). This provision, which is often referred to as the ''Delaney Clause,'' was added to the FD&C Act by the Food Additives Amendment of 1958 (Pub. L. 85–929). The Delaney Clause limits FDA's discretion to determine the safety of food additives, in that it 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. In *Public Citizen* v. *Young,* the DC Circuit Court of Appeals 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, which was subject to a similarly worded Delaney Clause for color additives, should be approved because it did not pose more than a de minimis cancer risk (831 F.2d 1108, 1122 (DC Cir. 1987); *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), on the grounds that they pose a de minimis cancer risk, is contrary to the provisions of the Delaney Clause).

The FD&C Act provides that FDA must by regulation prescribe the procedure by which a food additive regulation may be amended or repealed (see section 409(i) of the FD&C Act). Our regulation specific to the administrative actions for food additives provides that the Commissioner of Food and Drugs (the Commissioner), on his or her own initiative or on the petition of any interested person, may propose the issuance of a regulation amending or repealing a regulation pertaining to a food additive (see § 171.130(a) (21 CFR 171.130(a))). Our regulation, at § 171.130(b), further provides that any such petition must include an assertion of facts, supported by data, showing that new information exists with respect to the food additive or that new uses have been developed or old uses abandoned, that new data are available as to toxicity of the chemical, or that experience with the existing regulation or exemption may justify its amendment or repeal.

The specific food additive regulation at issue in the petition, § 172.515, lists synthetic flavoring substances and adjuvants that may be safely used in food in accordance with the conditions in the regulation. At issue in the petition are seven synthetic flavorings and adjuvants listed in this regulation: Benzophenone (also known as diphenylketone), ethyl acrylate, eugenyl methyl ether (also known as 4-allylveratrole or methyl eugenol), myrcene (also known as 7-methyl-3-methylene-1,6-octadiene), pulegone (also known as p-menth-4(8)-en-3-one, pyridine, and styrene. The petitioners assert that new data establish that these synthetic flavoring additives are carcinogenic and therefore not safe for use in food pursuant to the Delaney Clause.

B. Abandonment of Use of Styrene Authorized Under 21 CFR 172.515

Related to FAP 5A4810, in a document published in the *Federal Register* on June 15, 2016 (81 FR 38984), we announced that we filed a food additive petition (FAP 6A4817) proposing that we amend § 172.515 to no longer provide for the use of styrene as a synthetic flavoring substance and adjuvant in food because the use has been abandoned. Elsewhere in this issue of the *Federal Register*, we have published a final rule in response to FAP 6A4817 granting that petition and amending § 172.515 to no longer authorize the use of styrene as a synthetic flavoring substance and adjuvant in food because its use under § 172.515 has been permanently and completely abandoned. Because the final rule issued in response to FAP 6A4817 removes styrene from § 172.515—thereby taking one of the actions requested in this petition—the petitioners' request is moot, and it is neither necessary nor an efficient use of our resources to address the petitioners'

assertions regarding the safety of the food additive use of styrene that is no longer authorized. Therefore, we are denying as moot the request in FAP 5A4810 to remove styrene from § 172.515.

C. History of the Regulation of the Synthetic Flavoring Substances and Adjuvants

In the *Federal Register* of May 27, 1964 (29 FR 6957), FDA published a proposed rule to establish a regulation for synthetic flavoring substances and adjuvants used in food. The purpose of the proposed regulation was to identify those synthetic substances that may be safely used as flavoring substances or flavor adjuvants in food. The proposed regulation listed many synthetic flavoring substances and adjuvants in use at the time, including benzophenone, ethyl acrylate, eugenyl methyl ether, myrcene, pulegone, and pyridine. The proposed rule stated that, in reaching a conclusion about the safety of the substances listed in the proposed order, FDA relied upon experience based on the common use of these substances in food prior to 1958; the fact that many of the synthetic flavoring substances have a natural counterpart in food or in natural substances used to flavor foods; that metabolic and toxicity data representing studies made on selected flavoring substances were reviewed and safety established; and that relatively low and essentially self-limiting quantities are involved when these substances are used in food, consistent with good manufacturing practice. (29 FR 6957). In the *Federal Register* of October 27, 1964 (29 FR 14625), FDA issued a final rule based on this proposal with a few changes based on comments that were received and established this regulation in 21 CFR 121.1164. This regulation also limited the amount of the synthetic flavoring substance that could be added to food to the smallest amount necessary to achieve the desired flavoring effect. In the *Federal Register* of March 15, 1977 (42 FR 14302 at 14492), 21 CFR 121.1164 was redesignated § 172.515.

D. Summary and Context of Determination

We have evaluated the data and information submitted by the petitioners, as well as other relevant carcinogenicity data and information, and have determined the remaining six synthetic flavoring substances (*i.e.,* other than styrene) that are the subject of FAP 5A4810 are unlikely to pose a potential or significant carcinogenic risk for humans at the levels that these synthetic flavoring substances are used in foods, and that the use of these food additives is safe for human consumption. In other words, FDA has a reasonable certainty that the substances do no harm under the intended conditions of use (the standard for approving food additives). However, because data submitted by the petitioners demonstrate that these synthetic flavoring substances have been shown to induce cancer in animal studies, FDA cannot consider these synthetic flavoring substances to be safe as a matter of law because of the Delaney Clause, and must revoke the listings providing for the use of these synthetic flavoring substances and adjuvants, as described further in section III.

In making this determination, we reiterate the point, first made in our 1964 proposed rulemaking, that all of the synthetic flavoring substances that are the subject of the petition have a natural counterpart in food or in natural substances used to flavor foods. For example, benzophenone is present in grapes, ethyl acrylate is present in pineapple, eugenyl methyl ether (methyl eugenol) is present in basil, myrcene is present in citrus fruit, pulegone is present in peppermint, and pyridine is present in coffee. FDA's revocation of the listings providing for the use of these synthetic flavoring substances and adjuvants does not affect the legal status of foods containing natural counterparts or non-synthetic flavoring substances extracted from food, and there is nothing in the data FDA has reviewed in responding to the pending food additive petition that causes FDA concern about the safety of foods that contain natural counterparts or extracts from such foods.

III. Evaluation of Carcinogenicity

The petitioners assert that each of the synthetic flavoring substances (*i.e.,* benzophenone, ethyl acrylate, methyl eugenol, myrcene, pulegone, and pyridine) has been shown to induce cancer in animals by studies sponsored by the Department of Health and Human Services' National Toxicology Program (NTP). The petitioners also cite conclusions of the International Agency for Research on Cancer (IARC) and the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA), and assert that information that became available after these food additives were listed in § 172.515 demonstrates that ''they are not safe for use in food pursuant to the Delaney Clause''; however, we note that the conclusions from IARC and OEHHA are based primarily on results from the NTP studies. Thus, our review of whether the synthetic flavoring substances that are the subject of the petition induce cancer in humans or animals focused on results of the NTP studies, as well as other available relevant information discussed in this rule.

As part of our scientific review, we also evaluated the genotoxicity of the synthetic flavoring substances. Based on their biological activities, chemical carcinogens can be classified as genotoxic (directly DNA reactive) and non-genotoxic (not directly DNA reactive but operating through a secondary mechanism) (Ref. 1). In cancer risk assessments, the traditional assumption for chemicals that are genotoxic is that there is no threshold exposure level below which there is no risk of cancer and that there is a risk of cancer at any level of exposure. In contrast, non-genotoxic carcinogens are assumed to have a threshold of exposure level below which tumor development is not anticipated and the risk of cancer is negligible (Ref. 2).

Additionally, as part of our review, we calculated Margins of Exposure (MOE) for each of the six synthetic flavoring substances. The MOE is the ratio between a point of departure (*e.g.,* no-observed-adverse-effect-dose or benchmark dose) and estimates of human dietary exposure. As a risk characterization tool, the MOE can be used to provide information on the level of public health concern. The MOE is invaluable in risk management for chemicals present in food, when a health-based guidance level is impossible to derive, such as with genotoxic and carcinogenic contaminants and veterinary drug residues (Refs. 2 and 3). If the MOE is very large (such as greater than 10,000), it can be an indication of a low level of human health risk (Ref. 3).

We also estimated dietary exposure for the six synthetic flavoring substances using information from the 2015 Poundage and Technical Effects Survey that the Flavor and Extract Manufacturers Association (FEMA) collected from its member companies that formulate flavoring substances (Ref. 4). (The acronym FEMA, as used throughout this rule, refers to the Flavor and Extract Manufacturers Association. It should not be confused with the Federal Emergency Management Agency that commonly is referred to by this same acronym.) Every 5 years FEMA surveys its members to estimate the total volume of flavoring substances added to food, or ''poundage data.'' (The 2015 poundage data were the most recent available.) FEMA's members include flavor manufacturers, flavor users, flavor

ingredient suppliers, and others with an interest in the U.S. flavor industry. According to FEMA, their flavor manufacturing members produce more than 95 percent of flavors consumed in the United States.

To estimate dietary exposure to the synthetic flavoring substances, we used a ''per-capita times ten'' approach that conservatively assumes 10 percent of the population consumes 100 percent of the available flavoring substance. Because the FEMA poundage data include the total poundage for both synthetic and naturally-sourced flavoring substances, our estimates of dietary exposure assumed that all of the flavoring substances added annually to food are synthetic; thus, for most of these substances, actual exposure to these synthetic flavoring substances is less than our conservative exposure estimates (Refs. 5 and 6).

As explained in more detail later in this section, although there were findings of carcinogenicity in animal studies, none of the data in our evaluations of the six synthetic flavoring substances supports a finding that they are human carcinogens when consumed at the levels of intended use. Additionally, with the exception of the data concerning methyl eugenol, the data from the animal studies demonstrated that the modes of action (MOA) of carcinogenicity are not acting through mechanisms of genotoxic alterations and are not relevant to humans.

For methyl eugenol, the data showed evidence for a potential concern for carcinogenic risk to humans based on the findings that: (1) A metabolite of methyl eugenol was found to be genotoxic and able to covalently bind with DNA to form DNA adducts (a DNA adduct is a segment of DNA bound to a cancer causing chemical); (2) methyl eugenol-DNA adducts have been detected in human lung and liver tissues; and (3) there is a potential metabolic pathway by which methyl eugenol could metabolize to a reactive metabolite, under specific reaction conditions that then may proceed to tumor formation and carcinogenesis. However, there are no available clinical or epidemiological data reporting tumor formation and carcinogenicity from methyl eugenol exposure in humans.

Additionally, we concluded that the risk of carcinogenicity in humans from consumption of methyl eugenol added to food as a synthetic flavoring substance is further reduced by the following mitigating factors: (1) The metabolic pathway, in which methyl eugenol converts to a genotoxic metabolite subsequently leading to tumor formation, does not serve as the primary metabolic/detoxification pathway for methyl eugenol in humans and the amount of the genotoxic metabolite generated is dose-dependent, occurring at higher doses and (2) compared to the low levels of added synthetic methyl eugenol as a flavoring substance, the levels of methyl eugenol tested in the NTP animal studies were very high test doses that likely overwhelmed physiological conditions of normalcy and overloaded systemic repair systems.

In assessing the potential human carcinogenicity of methyl eugenol associated specifically with the use of synthetic methyl eugenol as a flavoring substance, we also considered data indicating that exposure to methyl eugenol from foods that naturally contain methyl eugenol (*e.g.,* basil and other spices/herbs) is significantly higher (approximately 488 times higher) than exposure expected from the addition of synthetic methyl eugenol as a flavoring substance, and that these foods have been ingested by humans for millennia without apparent harm (Ref. 7). Based on our review of published literature up to May 2018, there is no clinical or epidemiological evidence suggesting an association between the typical dietary consumption of food items that naturally contain methyl eugenol and carcinogenic effects.

In sum, although the data do not indicate that these synthetic flavoring substances pose a public health risk as a human carcinogen, because these six synthetic flavoring substances have been found to induce cancer in animal studies, the Delaney Clause requires that FDA consider these synthetic flavoring substances to be unsafe as a matter of law, and FDA must revoke the listings providing for the use of these synthetic flavoring substances.

Below is a summary of FDA's analysis of each of the six synthetic flavoring substances and adjuvants.

A. Benzophenone

1. Exposure

Under § 172.515, benzophenone is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with current good manufacturing practices (CGMP). FEMA estimated an annual production volume of 5 kilograms (kg) for benzophenone used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA also estimated that 133 kg of benzophenone are available for consumption annually in the United States from its natural presence in foods (Ref. 8). Thus, benzophenone is present from natural sources in the food supply (*e.g.,* grapes) at a level 27 times greater than that from its use as a flavoring substance and adjuvant. Using the FEMA poundage data (assuming all reported poundage is for the synthetically-prepared flavoring substance) and a ''per-capita times ten'' approach, we estimated dietary exposure from benzophenone added to food as a synthetic flavoring and adjuvant to be 0.43 micrograms per person per day (µg/p/d), or 7.2×10^{3} µg/kilogram body weight/d (µg/kg bw/d) for a 60 kg person (Refs. 6 and 9).

Benzophenone also is permitted for use as a plasticizer in rubber articles intended for repeated use under § 177.2600. The upper-bound limit to the dietary exposure for benzophenone from this use is estimated to be 45 µg/p/d. This estimate assumes that 100 percent of an individual's diet is processed using rubber articles containing benzophenone as a plasticizer. While the exposure estimate for the use of benzophenone as a plasticizer in repeat use rubber articles is an overestimate of the actual exposure from this use, the estimated exposure is greater than that from the use of benzophenone as a flavoring substance by a factor of approximately 500. Thus, the combined exposure to benzophenone from its uses as a flavoring substance and as a plasticizer in food contact applications was estimated to be no more than 45 µg/p/d, or 0.75 µg/kg bw/d (Refs. 5 and 9).

2. Toxicology Studies

FDA reviewed data from 2 NTP-sponsored 105-week carcinogenic bioassays on benzophenone in F344/N rats and B6C3F1 mice. In these studies, the rats and mice were administered feed containing benzophenone at 0, 312, 625, or 1,250 parts per million per day (ppm/d) or milligrams per kilogram of feed/day (mg/kg/d). This dosing is equivalent to average daily doses of approximately 15, 30, and 60 mg benzophenone/kg bw to male rats and 15, 30, and 65 mg/kg bw to female rats; equivalent to average daily doses of approximately 40, 80, and 160 mg/kg bw to male mice and 35, 70, and 150 mg/kg bw to female mice (Ref. 9).

The NTP reported several carcinogenicity findings from these studies. They noted that there was some evidence of carcinogenicity due to increased incidence of renal (kidney) tubular tumors in treated male rats and increased incidence of mononuclear cell leukemia (MNCL) in all treated female rats. The mean incidence of MNCL in

the 625 ppm female dose group was significantly greater than that in the control female rats. The NTP also reported some evidence of carcinogenic activity in male mice based on increased incidence of hepatocellular (liver) neoplasms and some evidence of carcinogenicity in female mice based on increased incidence of histiocytic (originating from blood cells) sarcomas. Results showed that benzophenone produced tumors at the two highest doses in the studies. Occurrence of the key tumor types (*i.e.,* those tumor types the NTP considered to constitute ''some evidence'' of carcinogenicity) in animals at the lowest dose was not significantly different from that of the control groups. The NTP classified the occurrence of the key tumor types as constituting some evidence of carcinogenic activity rather than being clear evidence of carcinogenic activity (NTP's highest level of evidence of carcinogenicity). Benzophenone also was tested in several genotoxicity assays and found to be non-genotoxic.

Based on results from the NTP studies, FDA concluded that, under the conditions of the 2-year NTP bioassays, benzophenone induced renal tubular tumors in male rats and hepatocellular tumors in male mice (Ref. 9).

3. Risk Characterization

Based on the results of the NTP 2-year carcinogenicity studies we concluded that benzophenone induced cancer in animals under the test conditions of the studies. However, benzophenone is not genotoxic and unlikely to produce cancer through a direct DNA-reactive mechanism. Chronic progressive nephropathy (CPN, a spontaneous age-related disease that occurs commonly in rats) may be involved in benzophenone inducing renal tumors in rats; however, CPN as a MOA, a biologically plausible sequence of key events leading to an observed endpoint supported by robust experimental observations and mechanistic data (Ref. 10), for renal tumors in humans has not been established. Regarding the incidence of MNCL in female F344/N rats, we determined that it was not dose-dependent and that the incidence of this tumor in the control rats was outside the historical range. Therefore, we concluded that the occurrence of renal tumors in this study is not related to treatment with benzophenone. Additionally, MNCL is species- and strain-specific to the F344/N rat, and of little or no relevance to humans (Ref. 9).

Regarding the results from the mouse study, several authors have observed that hepatocellular neoplasms seen in 2-year bioassays in B6C3F1 mice typically are secondary responses to chronic hepatic toxicity and regenerative cellular proliferation or hypertrophy as a function of dose (Ref. 9). Evidence of hepatotoxicity in short duration studies also has been shown to be a good predictor of hepatic neoplasia in chronic studies and the higher susceptibility of the male mouse (Ref. 9). Although there is no definitive MOA for the development of benzophenone-associated liver tumors in the NTP study, the B6C3F1 male mouse has been shown to have a high incidence of spontaneously-occurring hepatocellular tumors, which is elevated after chemical exposure. Introduction of high doses of benzophenone may produce hepatotoxicity that exacerbates this propensity toward tumor development and results in their increased occurrence by a non-genotoxic mechanism. Although rarely reported in NTP studies, histiocytic sarcomas observed in the B6C3F1 mice have been reported to occur at a mean incidence of 5.5 percent in female B6C3F1 mice used as controls in 2-year carcinogenicity studies conducted at Bayer AG, Institute of Toxicology. This result was based on historical data accumulated over a 10-year period (1986–1996) and is in line with the 6 percent occurrence observed in the high dose (1,250 ppm) group in the benzophenone NTP study. Other authors also reported similar findings in B6C3F1 mice, with incidences of 3.5 percent and 5.5 percent in control males and females, respectively. Histiocytic sarcomas are rarely reported in humans, accounting for less than 1 percent of all the neoplasms reported in the lymph nodes or soft tissues. The histiocytic sarcomas identified in the female mice in the NTP study were not dose related (*i.e.,* 5/50 at 625 ppm and 3/50 at 1,250 ppm) and were found only at dose levels that induced overt toxicity (Ref. 9).

The lowest test dose (312 ppm) in the NTP 2-year studies was a dose at which no statistically significant treatment-related increase in tumor incidence was reported in rats or mice. This finding suggests that there may be a threshold level below which benzophenone does not induce tumors in rodents. Additionally, there is a large margin of exposure (MOE; 2.1×10^6 for rats, 4.7×10^6 for male mice, and 5.6×10^6 for female mice) between the lowest test dose and the estimated dietary exposure of 0.43 µg benzophenone/p/day (equivalent to 7.2×10^{-3} µg/kg bw/day) from its use as a flavoring substance. When benzophenone is used as a plasticizer in repeat use rubber articles exposed to food, the MOE for male and female rats is calculated to be 2×10^4 and for male and female mice, 5.3×10^4 and 4.7×10^4, respectively. Although these MOE values are lower than those for benzophenone's use as a synthetic flavoring substance, they are still sufficient to ensure an acceptable margin of safety (Ref. 9). It should also be noted that these results are based on estimated worst-case dietary exposure of 45 µg/person/d (0.75 µg/kg bw/d) from its use as a plasticizer (Ref. 5) and actual MOEs for this use probably would be higher. Considering these findings in a weight-of-evidence analysis, we concluded that benzophenone is unlikely to induce tumors in humans at current use levels as a synthetic flavoring substance and adjuvant in food (Ref. 9).

B. Ethyl Acrylate

1. Exposure

Under § 172.515, ethyl acrylate is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with CGMP. FEMA estimated an annual production volume of 18 kg for ethyl acrylate used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA also estimated that 9.2 kg of ethyl acrylate are available for consumption annually in the United States from its natural presence in foods (*e.g.,* pineapple) (Ref. 8). Thus, ethyl acrylate is present in foods from natural sources at 50 percent of the level from its use as a flavoring substance. Using the FEMA poundage data (assuming all reported poundage is for the synthetically-prepared flavoring substance) and a ''per-capita times ten'' approach, we estimated dietary exposure from ethyl acrylate's use as a synthetic flavoring substance and adjuvant in food to be 1.5 µg/person/d, or 0.025 µg/kg bw/d for a 60 kg person (Refs. 6 and 11).

2. Toxicology Studies

FDA reviewed data from 2 NTP-sponsored 103-week carcinogenic bioassays on ethyl acrylate in F344/N rats and B6C3F1 mice. In these studies, rats and mice were administered ethyl acrylate at 0, 100, or 200 mg/kg bw by gavage 5 days per week. The NTP reported carcinogenicity findings were confined to the forestomach of rats and mice. They also reported that the occurrence of these forestomach tumors had a statistically positive trend compared to the control animals. Ethyl acrylate also was tested in several genotoxicity studies. Based on the available data from these studies, we

concluded that ethyl acrylate is not genotoxic (Ref. 11).

We also concluded that under the test conditions of NTP's 2-year hazard assessment studies ethyl acrylate is a rodent carcinogen. Evidence, however, supports the findings that these tumors were produced by a non-genotoxic mechanism (Ref. 11).

3. Risk Characterization

The tumors observed in the NTP study were initiated by administering bolus doses of ethyl acrylate by gavage onto the forestomach of the treated rats and mice, which resulted in irritation, inflammation, and hyperplasia of the forestomach mucosa. Repeated dosing over a 2-year period exacerbated this irritation and resulted in the development of papillomas and carcinomas, which were confined to the forestomach. No other treatment-related tumors were observed in the animals. Forestomach tumors were observed at both doses tested (100 mg/kg bw and 200 mg/kg bw) in both male and female mice and rats. Humans do not have a forestomach and a human counterpart for the forestomach does not exist. The function of the rodent forestomach is to store and concentrate feed; therefore, high concentrations of ethyl acrylate were present in the forestomach over the duration of the 2-year study. This concentration effect precluded our determining a no-significant-effect-level for the occurrence of the forestomach tumors. Therefore, we cannot make an MOE comparison between a no-effect-dose level for significant incidences of tumors and the estimated dietary exposure of ethyl acrylate as a synthetic flavoring substance and adjuvant in food (1.5 µg ethyl acrylate/p/d, or 0.025 µg/kg bw/d) (Ref. 11).

The 2-year NTP studies were conducted at doses higher than the expected exposures for flavoring substances. In general, flavoring substances have significantly lower dietary exposures than the doses used in 2-year carcinogenicity studies. For example, the lowest dose of ethyl acrylate tested in the NTP studies was 100 mg/kg bw, or approximately 1.8×10^6 times greater than the estimated dietary exposure from its use as a synthetic flavoring substance and adjuvant in food (Ref. 11).

Importantly, the NTP Board of Scientific Counselors Report on Carcinogens (RoC) Subcommittee concluded, based on the totality of the evidence, that ethyl acrylate should not be considered a human carcinogen (Ref. 12). We concur with the RoC and concluded that ethyl acrylate is a non-genotoxic rodent carcinogen with a carcinogenic effect limited to the rodent forestomach (a rodent-specific organ) due to chronic irritation. This MOA is not relevant to humans and, at the current intake level, there is no concern of carcinogenicity from the intake of ethyl acrylate intentionally added to food as a flavoring substance and adjuvant (Ref. 11).

C. Eugenyl Methyl Ether (Methyl Eugenol)

1. Exposure

Under § 172.515, methyl eugenol is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with CGMP. FEMA estimated an annual production volume of 86 kg for methyl eugenol used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA also estimated that 447,450 kg of methyl eugenol are available for consumption annually in the United States from its natural presence in foods (*e.g.,* basil) (Ref. 8). The 69th Joint Food and Agriculture Organization/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) estimated an upper bound annual volume for methyl eugenol of 41,992 kg from its natural presence in herbs and spices. The most significant difference between the two estimates is that FEMA presumed a maximum content of methyl eugenol in basil of 4.1 percent, whereas JECFA presumed a maximum content of 0.118 percent (Refs. 5 and 8). Natural sources of basil have varying levels of methyl eugenol. It is unlikely, however, that most basil used in the United States would consistently have levels as high as 4.1 percent and, as such, JECFA's estimate of the amount of methyl eugenol from natural sources is suitably conservative and representative of probable consumption. Using the JECFA estimate, methyl eugenol is estimated to be present in the food supply from natural sources at a level 488 times greater than that from its use as a synthetic flavoring substance or adjuvant in food. Using the FEMA poundage data (assuming all reported poundage is for the synthetically prepared flavor) and a ''per-capita times ten'' approach, we estimated dietary exposure from methyl eugenol's use as a synthetic flavoring substance and adjuvant in food to be 7.4 µg/person/d, or 0.12 µg/kg bw/d for a 60 kg person (Refs. 6 and 13).

2. Toxicology Studies

FDA reviewed data from 2 NTP-sponsored 2-year carcinogenicity bioassays on methyl eugenol in F344/N rats and B6C3F1 mice. In these studies, methyl eugenol was administered to the animals at 0, 37, 75, or 150 mg/kg bw by gavage, 5 days per week, for 105 weeks. These test doses are 220,000 to 890,000 times higher than the estimated human dietary exposure from its use as a flavoring substance.

The NTP reported significantly increased incidence of liver tumors (combined adenomas or carcinomas), compared to the concurrent control groups, occurring in a dose-dependent manner across the treatment groups in both genders of rats and mice. Although the mortality in some treated groups was higher than 50 percent, tumors were the main cause of death in these groups. Further, most deaths occurred late in the studies. Another type of tumor, glandular stomach neuroendocrine neoplasms, were found in both genders of rats, but in only two male mice. The NTP, JECFA, and FDA do not consider these glandular stomach neuroendocrine neoplasms relevant to tumor formation in humans due to considerations of the mechanism of development of these neoplasms. Based on the overall data, we concluded that methyl eugenol, under the test conditions of the NTP 2-year carcinogenicity bioassays, induced cancer in rodents (Ref. 13).

Regarding the genotoxicity potential of methyl eugenol, results from several genotoxicity assays were negative; however, in testing systems that provided adequate metabolic activation, specifically 1′-hydroxylation and sulfonation, or those systems directly testing the 1′-hydroxyl metabolite of methyl eugenol, positive genotoxic effects were observed.

There is evidence showing that methyl eugenol treatment leads to the formation of covalent DNA adducts in vitro and in vivo. In cancer risk assessment, the formation of DNA adducts is a biomarker of exposure and suggestive of potential cancer risk. However, the observation of adducts itself should not be used to predict cancer. The relevance of DNA adducts for cancer assessment should be investigated in the context of other information, such as the quantity and persistency of the adducts. The level of methyl eugenol-specific adducts was shown to be dose-dependent in experimental animals. Therefore, since human dietary consumption of methyl eugenol from use as a synthetic flavoring substance in food is much lower than the dose received by the animals in the NTP studies, much lower levels of DNA adducts would be formed in humans compared to that in the test

animals. Additionally, there is evidence that the formation of these adducts requires specific metabolic activation of methyl eugenol (*i.e.,* hydroxylation followed by sulfonation, leading to the formation of 1′-sulfooexymethyleugenol, the ultimate metabolite that binds to DNA). Based on the physiology-based pharmacokinetic model of methyl eugenol, this pathway is not a major metabolic pathway in humans. Even after hydroxylation occurs, the hydroxylated intermediates can be eliminated by glucuronization and oxidation, so that only a trace amount of ingested methyl eugenol is metabolized to 1′-sulfooexymethyleugenol. In regard to the persistence of the adducts, there is evidence showing that in rats given methyl eugenol, the levels of methyl eugenol-specific adducts reduced after the treatment was stopped, suggesting that these adducts are repairable with considerable low persistency (Ref. 13).

There are only few studies measuring methyl eugenol-specific DNA adducts in humans. The adducts have been detected in 150 of 151 human liver biopsy samples and 10 of 10 tested human lung biopsy samples, indicating that the bioactive metabolites form in these subjects with typical dietary exposure, and are capable of binding with human DNA. However, these human data have limitations. We note that all but one the human tissue donors in these studies were patients with cancer or chronic liver diseases, who may have DNA-repair deficiencies, compromised detoxification pathways, or weakened control mechanisms that prevent the promotion of carcinogenesis from DNA adducts, whereas such control mechanisms would be expected to be operable in healthy humans. Therefore, it is difficult to extrapolate DNA-adduct results found in these unhealthy subpopulations to the general healthy population (Ref. 13).

3. Risk Characterization

In our evaluation of the carcinogenic potential of methyl eugenol in humans using a weight-of-evidence approach, we concluded that a genotoxic MOA is likely involved in the carcinogenicity observed in the NTP animal studies. This MOA involves formation of a bioactivated metabolite that forms DNA-adducts that leads to subsequent cancer initiation and development. Current scientific data on methyl eugenol suggest that bioactivation to the DNA-reactive metabolite, DNA adduct formation, and subsequent tumor formations are dose-dependent. Although methyl eugenol-specific DNA adducts have been identified in hospitalized subpopulations, there are no clinical or epidemiological data that provide concrete evidence that methyl eugenol is a human carcinogen. In the general healthy population, DNA-repair mechanisms and damage-response pathways may effectively prevent cancer development from an initiation event such as a DNA adduct. Therefore, the extremely low level of DNA adducts formed in humans from dietary exposure to methyl eugenol as an added food flavoring substance likely is below a threshold level necessary for subsequent cancer development. However, the current science is inadequate to quantitate the carcinogenic potential risk (if any) of methyl eugenol in humans (Ref. 13).

Carcinogenicity data on methyl eugenol also demonstrated that non-genotoxic MOAs for the observed tumors in animals, especially in mice, may be operating in conjunction with the genotoxic MOA. However, data for the non-genotoxic MOA are insufficient (Ref. 13).

The MOE for synthetic methyl eugenol as a flavoring substance and adjuvant in food is very large. Two dose-response assessments have been conducted to derive a point of departure for the liver carcinogenicity of methyl eugenol; both derived a lower bound benchmark dose ($BMDL_{10}$) based on data from the NTP bioassays. Using the more conservative $BMDL_{10}$ (7.7 mg/kg/d), and the estimated dietary exposure of methyl eugenol as a flavoring substance (0.12 μg/kg bw), the MOE is approximately 6.4×10^4. This MOE is based on an estimated dietary exposure that assumed 100 percent of the reported poundage data are exclusively synthetic methyl eugenol. Thus, the actual MOE for synthetically prepared methyl eugenol added to foods likely is larger. Although the carcinogenic potential cannot be definitively ruled out, this large MOE translates into a very small risk for carcinogenicity in humans and a low public health concern (Ref. 13).

As for methyl eugenol from natural sources, other components in such sources may modulate bioactivation and/or detoxification, so the toxicity data related to the use as a synthetic flavoring substance may not be relevant to its presence from natural sources. For example, a flavonoid derived from basil extracts, nevadensin, was found to be a sulfotransferase inhibitor, and it significantly reduced methyl eugenol-induced DNA adduct formation in F344/N rats (Ref. 13).

In conclusion, although there is evidence of genotoxicity for a bioactive metabolite of methyl eugenol, we concluded based on currently available scientific evidence that, despite the potential carcinogenic concern and lack of definitive quantitative cancer risk measurement, such risk in humans is mitigated by factors such as low exposure from its use as a flavoring substance, pharmacokinetics/metabolism, DNA-repair mechanisms, and the lack of clinical and epidemiological evidence of the carcinogenic effect in humans from oral exposure to methyl eugenol. Therefore, it is unlikely that consumption of methyl eugenol presents a risk to public health from use as a flavoring substance.

D. Myrcene

1. Exposure

Under § 172.515, myrcene is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with CGMP. FEMA estimated an annual production volume of 860 kg for myrcene used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA also estimated that 14,177,215 kg of myrcene are available for consumption annually in the United States from its natural presence in foods (*e.g.,* citrus juices) (Ref. 8). Thus, myrcene is present naturally in foods at a level 16,500 times greater than that from use as a flavoring substance and adjuvant. We estimated dietary exposure to myrcene as a synthetic flavoring substance using the FEMA poundage data (assuming all reported poundage is for the synthetically prepared flavoring substance) and a ''per-capita times ten'' approach to be 74 μg/person/d, or 1.23 μg/kg bw/d for a 60 kg person (Refs. 6 and 14).

2. Toxicology Studies

FDA reviewed data from 2 NTP-sponsored carcinogenicity bioassays on myrcene (β-myrcene) in F344/N rats and B6C3F1 mice. In the rat study, male and female rats were administered 0, 0.25, 0.50 or 1.0 g myrcene/kg bw by gavage, 5 days per week for up to 105 weeks. Results from the study showed increased incidence of renal tubule tumors in both sexes. All high dose (1 g/kg bw) male rats died prior to the end of the study due to renal toxicity. Incidence of nephrosis were significantly increased in all dosed male and female rats when compared to controls. Incidence of CPN were significantly increased in all myrcene-treated female rats but not male rats. There also was significantly increased incidence of nephrosis in all myrcene-

treated male and female rats compared to controls. However, incidence of mineralization of renal papilla also was significantly increased in all dosed male rats but not in female rats. Based on increased incidence of renal tubule neoplasms, NTP concluded that there was clear evidence of carcinogenic activity of myrcene in male F344/N rats and equivocal evidence of carcinogenic activity of myrcene in female rats (Ref. 14).

In the NTP mouse study, male and female mice were administered 0, 0.25, 0.50 or 1.0 g myrcene/kg bw by gavage, 5 days per week for up to 104 (females) and 105 weeks (males). Based on increased incidence of liver neoplasms, NTP concluded that there was clear evidence of carcinogenic activity of myrcene in male mice and equivocal evidence of carcinogenic activity of myrcene in female mice (Ref. 14).

Myrcene also was tested in several in vivo and in vitro genotoxicity assays sponsored by the NTP. The NTP concluded that myrcene was not genotoxic based on the negative Ames assays (*Salmonella typhimurium* (*S. typhimurium)* and *Escherichia coli (E. coli)*) and in vivo micronucleus assays in male and female B6C3F1 mice (Ref. 14).

Based on our evaluation of the data in the NTP 2-year myrcene studies, we concluded that, under the test conditions of the studies, myrcene induced renal tubular tumors in F344/N rats and hepatocellular tumors in B6C3F1 mice. We also concluded that myrcene is non-genotoxic (Ref. 14).

3. Risk Characterization

Our review of relevant scientific data and information suggests that myrcene may be operating through multiple MOAs to induce kidney and liver tumors in rodents. While, a definitive MOA for the induction of tumors by myrcene in rodents has not been established, because myrcene is not genotoxic, the induction of rodent tumors likely is occurring through an indirect non-DNA mediated MOA. One potential MOA in male and female rats is an unusual nephrosis. Another potential MOA, α2u-globulin (a low molecular-weight protein synthesized in the male rat liver) hyaline nephropathy, and renal tubular hyperplasia may collectively contribute to the development of renal tubule neoplasia in male rats following myrcene treatment (the α-2u-globulin nephropathy occurs only in male rats and is not operative in humans) (Ref. 14).

The B6C3F1 mouse strain used in the NTP-sponsored study with myrcene is known to have a high spontaneous background incidence of liver neoplasms and is a sensitive strain for the induction of liver tumors. The observed hepatocellular tumors in myrcene-dosed mice exceeded concurrent and historical controls. The MOA for the induction of hepatocellular tumors in myrcene dosed mice is not well understood. We are not aware of any robust mechanistic studies conducted to determine the MOA(s) responsible for the induction of hepatocellular neoplasia reported in myrcene-treated mice (Ref. 14).

In the NTP 2-year rat study, increased incidence of renal tubular tumors was observed in all doses of myrcene treated male rats. Because a no significant effect dose level was not observed in this study, we derived a $BMDL_{10}$ of 64,000 µg/kg bw/d based on the most sensitive endpoint, the combined renal tubular adenomas and carcinomas in male rats. Based on this $BMDL_{10}$ and the estimated dietary exposure to myrcene, we calculated an MOE of 5.2×10^4 (Ref. 14).

Using a weight-of-evidence analysis, we concluded that myrcene is unlikely to induce tumors in humans at its current exposure level when used as a synthetic flavoring substance and adjuvant in food based on the following: (1) Myrcene is non-genotoxic; (2) the MOA for kidney tubule tumors likely involves multiple MOAs that may include renal toxicity (nephrosis), α2u-globulin nephropathy (a mechanism not operative in humans), and hyperplasia in male rats. In female rats, nephrosis and hyperplasia are likely MOAs; (3) B6C3F1 mice are prone to spontaneous hepatocellular adenomas, carcinomas, and hepatoblastomas with high background tumor incidence, and (4) a MOE of 5.2×10^4 indicates a low risk concern from a public health point of view (Ref. 14).

E. Pulegone

1. Exposure

Under § 172.515, pulegone is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with CGMP. FEMA estimated an annual production volume of 6 kg for pulegone used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA estimated that 866 kg of pulegone are available for consumption annually in the U.S. from its natural presence in foods (*e.g.,* mint) (Ref. 8). Thus, pulegone is present from natural sources in the food supply at a level 144 times greater than that from use as a flavoring substance and adjuvant. Using FEMA poundage data (assuming all reported poundage is for the synthetically prepared flavor) and a ''per-capita times ten'' approach, we estimated dietary exposure from pulegone's use as a synthetic flavoring substance and adjuvant in food to be 0.5 µg/person/d, equivalent to 0.008 µg/kg bw/d for a 60 kg person (Refs. 6 and 15).

2. Toxicology studies

FDA reviewed data from 2 NTP-sponsored 2-year carcinogenicity bioassays on pulegone in F344/N rats and B6C3F1 mice. In the rat study, pulegone was administered by gavage at 0, 18.75, 37.5, or 75 mg pulegone/kg bw to male rats and 0, 37.5, 75, or 150 mg pulegone/kg bw to female rats 5 days a week for up to 104 weeks. The NTP reported that, in female rats, the primary tumors observed were urinary bladder papillomas and carcinomas. In male rats, no urinary bladder neoplasms were reported. Only transitional epithelial hyperplasia was observed in the pulegone-treated male rats at the lowest dose tested; no epithelial hyperplasia was observed in male rats at the mid or high doses. Pulegone administration also was associated with the occurrence of non-neoplastic lesions in the liver and nose of male and female rats, and in the forestomach of male rats. The NTP concluded that under the conditions of the experiment, there was no evidence of carcinogenic activity of pulegone in male F344/N rats and clear evidence of carcinogenic activity of pulegone in female F344/N rats based on increased incidence of urinary bladder neoplasms.

In the mouse study, pulegone was administered by gavage at 0, 37.5, 75 or 150 mg/kg bw 5 days a week for 105 weeks. The NTP reported that the primary tumors observed in the study were liver neoplasms in male and female mice. The NTP concluded that under the conditions of the experiment, there was clear evidence of carcinogenic activity of pulegone in male and female B6C3F1 mice.

Pulegone also was tested in several in vitro and in vivo genotoxicity assays. Overall, results were mostly negative. However, NTP concluded that pulegone is genotoxic based on a single positive result in the Ames Assay in *S. typhimurium* strain TA 98 and *E. coli* strain WP2 uvrA/PKM101 in the presence of metabolic activation.

Based on the findings of statistically significant increased incidence of urinary bladder papilloma and carcinoma in female F344/N rats and liver neoplasms in B6C3F1 male and female mice in the 2-year NTP

bioassays, we concluded that under the conditions of the 2 NTP studies, pulegone is a rodent carcinogen. Based on the totality of evidence from available genotoxicity studies, we also concluded that pulegone is likely non-genotoxic (Ref. 15).

3. Risk Characterization

According to NTP, the dose-related increase in the incidence of urinary bladder neoplasms in female rats was most likely related to the genotoxic activity of pulegone. However, we concluded that pulegone likely is non-genotoxic based on negative results in the majority of genotoxicity studies, along with a lack of available evidence reporting that DNA adducts related to pulegone treatments are formed. This suggests that the urinary bladder neoplasms observed in female F344/N rats treated with pulegone were caused by a non-genotoxic MOA.

Urinary bladder carcinogenesis likely is occurring in the rat through cytotoxicity as a result of chronic exposure to high concentrations of pulegone and its metabolites, followed by regenerative urothelial cell (a cell type that lines much of the urinary tract) proliferation, that further led to urothelial tumors (Ref. 15). Da Rocha et al. (2012) (Ref. 16) concluded that the carcinogenic MOA for urinary bladder tumors was not relevant to humans, based on the assertion that humans would never be exposed to pulegone long enough to develop hyperplasia because pulegone is highly volatile, noxious, and a nasal irritant, and that genotoxicity of pulegone has not been demonstrated.

The metabolic fate of pulegone has been studied extensively in rodents and is well understood. Pulegone is metabolized by multiple pathways in the rodent. One important intoxication (bioactivation) pathway involves the formation of menthofuran, the proximate toxic metabolite of pulegone, which is further oxidized in the liver to yield γ-ketoenal, 8-pulegone aldehyde. γ-ketoenal, 8-pulegone aldehyde is the ultimate toxic metabolite of pulegone in rodents. In general, at dose levels at or below 80 mg/kg bw, cellular concentrations of pulegone and its metabolites are effectively detoxified by conjugation with glutathione and glucuronic acid in rodents (Ref. 15).

In a human metabolism study in which pulegone was administered orally at doses of 0.5 to 1 mg/kg bw, 10-hydroxypulegone, not menthofuran, was the major metabolite. In this study, 10-hydroxypulegone was conjugated with glucuronic acid or sulfuric acid and detoxified. Based on the limited, available human metabolism data, the toxic metabolite of pulegone, menthofuran, is not formed at toxicologically significant levels in humans at the dietary exposure levels expected from the use of pulegone as a flavoring substance (Ref. 15).

Protein adduct formation and glutathione depletion have been postulated as potential MOAs of pulegone via menthofuran formation, which could cause cytotoxicity and chronic cell proliferation, and ultimately lead to liver neoplasms. In vivo and in vitro studies showed an association between hepatocellular damage caused by menthofuran and its metabolic activation to γ-ketoenal, 8-pulegone aldehyde and covalent binding to target organ proteins. Further, p-cresol, another pulegone metabolite produced in rodents given high doses of pulegone, depletes glutathione levels. This may lead to chronic regenerative cell proliferation, which may be related to the liver carcinogenicity observed in experimental B6C3F1 mice (Ref. 15)

Considering genotoxicity data, metabolism, MOA, and the sensitivity of the B6C3F1 strain to develop hepatocellular tumors, the mouse liver tumors likely are not relevant to humans at the current use level of pulegone as a synthetic flavoring substance and adjuvant in food (Ref. 15).

An MOE was calculated using the no-significant effect level at which no treatment-related tumors were reported in the 2-year NTP mouse study of pulegone in male rats (*i.e.,* no significant effect level (18.75 mg/kg bw, equivalent to 13.39 m g/kg bw/day)). This dose was selected because in female rats, combined incidence of urinary bladder papilloma or carcinoma (a rare tumor) was significantly increased at the high dose (150 mg/kg bw), exceeding historical control ranges for 2-year corn oil gavage studies and concurrent controls. In male mice, the incidence of hepatocellular adenomas in the 37.5 mg/kg bw dose group exceeded that in the concurrent and historical control ranges for 2-year corn oil gavage studies. In addition, in female mice, the incidence of hepatocellular adenomas in the 37.5 mg/kg bw dose group exceeded that in the concurrent and historical control ranges for 2-year corn oil gavage studies. Although not statistically significant, these occurrences may be biologically relevant, given that they exceeded those of the historical and concurrent controls, and there were statistically significant increases in some proliferative non-neoplastic lesions in the liver of male mice at this dose. The MOE based on the estimated dietary exposure of 0.5 μg/p/d (equivalent to 0.008 μg/kg bw/d) for pulegone as a flavoring substance in humans is 1.7×10^6, which indicates a very low potential carcinogenic risk for humans (Ref. 15).

Using a weight-of-evidence analysis considering that: (1) Pulegone is non-genotoxic; (2) pulegone has a potential cytotoxicity MOA; (3) available data suggest a dose-dependent, metabolic activation of pulegone in humans and rodents, an indication of a threshold effect; (4) there is a no-significant effect level below which no tumors were formed in the 2 NTP year studies; (5) dietary exposure from use as a synthetic flavoring substance added to food is low with a MOE of 1.7×10^6, we concluded that pulegone at its current use level as a synthetic flavoring substance and adjuvant in food, is unlikely to induce urinary bladder cancer and liver neoplasms in humans and does not pose a public health concern (Ref. 15).

F. Pyridine

1. Exposure

Under § 172.515, pyridine is permitted for use as a synthetic flavoring substance and adjuvant in foods in accordance with CGMP. FEMA estimated an annual production volume of 27 kg for pyridine used as a flavoring substance and adjuvant in food based on information from the 2015 FEMA Poundage and Technical Effects Survey (Ref. 4). FEMA also estimated that 73,861 kg of pyridine are available for consumption annually in the U.S. from its natural presence in foods (*e.g.,* coffee) (Ref. 8). Thus, pyridine is present from natural sources in the food supply at a level 2,736 times greater than that from use as a flavoring substance. Using the FEMA poundage data (assuming all reported poundage is for the synthetically prepared flavoring substance) and a ''per-capita times ten'' approach, we estimated dietary exposure from pyridine's use as a synthetic flavoring substance and adjuvant in food to be 2.3 μg/person/day, or 0.038 μg/kg bw/d for a 60 kg person (Refs. 6 and 17).

2. Toxicology studies

FDA reviewed data from 3 NTP-sponsored 2-year carcinogenicity bioassays on pyridine in F344/N rats, Wistar rats, and B6C3F1 mice. In the F344/N rat study, pyridine was administered in drinking water at 0, 100, 200, or 400 ppm (mg pyridine/kg drinking water) for 104 (males) and 105 (females) weeks. These dose levels were equivalent to doses of 7, 14, or 33 mg pyridine/kg bw/d, respectively. The

NTP reported a statistically significant increased incidence of renal tubule adenomas and renal tubule hyperplasia only in the high dose F344/N male rats. In addition, NTP reported significantly elevated incidences of MNCL in F344/N female rats at the 200 ppm and 400 ppm dose levels. MNCL is a commonly occurring spontaneous neoplasm in untreated, older F344/N rats. One study found that MNCL occurs in untreated, aged F344/N rats at a high and variable rate; that MNCL as a lesion is uncommon in most other rat strains; and the background incidence of MNCL in F344/N rats has increased significantly over the years (Ref. 17).

Recognizing the species specificity and high background levels of MNCL in F344/N rats, the NTP conducted a 2-year carcinogenicity study in male Wistar rats (a rat strain that does not have a high background of MNCL neoplasms). In this study, pyridine was administered in drinking water at 0, 100, 200, or 400 ppm for 104 weeks to male Wistar rats. These dose levels were equivalent to doses of 8, 17, or 36 mg pyridine/kg bw/d. The study showed no increased incidences of MNCL in any of the treatment groups. The NTP reported a statistically significant increased incidence of interstitial cell adenomas in the 400 ppm dose group. Observed increased incidence of interstitial cell adenomas of the testes in Wistar rats exposed to 400 ppm pyridine were marginally above the historical control range. A statistically significant increased incidence of kidney hyperplasia was observed at the 100 ppm dose group, along with increased incidence of kidney adenomas that were not statistically significant. There also was increased incidence of nephropathy in all pyridine-treated Wistar rats as well as in the controls (Ref. 17).

The NTP concluded that under the conditions of the 2-year F344/N rat oral drinking water study there was some evidence of carcinogenic activity of pyridine in male F344/N rats based on increased incidence of renal tubule neoplasms and equivocal evidence of carcinogenic activity of pyridine in female F344/N rats based on increased incidence of MNCL. The NTP considered the increased incidence of interstitial cell adenomas of the testes in the Wistar rat study to be equivocal evidence for carcinogenicity.

In the mouse study, pyridine was administered in drinking water to male B6C3F1 mice at concentrations of 0, 250, 500 or 1,000 ppm (doses equivalent to 35, 65, or 110 mg pyridine/kg bw/d, respectively) for 104 weeks. Groups of female B6C3F1 mice were administered pyridine at doses of 0, 125, 250 or 500 ppm (doses equivalent to 15, 35, or 70 mg pyridine/kg bw/d, respectively) in drinking water for 105 weeks. The NTP reported statistically significant increased incidence of hepatocellular carcinomas at all dose levels in the male and female mice and concluded that there was clear evidence of carcinogenic activity of pyridine in male and female B6C3F1 mice.

Pyridine also was tested in several in vitro and in vivo genotoxicity assays. The NTP concluded that pyridine was non-genotoxic. Based on evidence from available studies, we also concluded that pyridine is non-genotoxic (Ref. 17).

Under the test conditions of the 2-year NTP studies, we concluded that pyridine is a rodent carcinogen based on the observed pyridine-induced renal tumors in male F344/N rats and pyridine-induced liver tumors in B6C3F1 mice (Ref. 17).

3. Risk Characterization

Our review of relevant scientific data and information suggests that pyridine may be operating through multiple MOAs in its capability to induce kidney and liver tumors in rodents. A definitive MOA for the induction of tumors in rodents has not been established. However, because pyridine is not genotoxic, the induction of rodent tumors likely is occurring through an indirect non-DNA mediated MOA.

While NTP discounted the kidney neoplasms observed in the F344/N rats as being associated with an α2μ-globulin MOA, we concluded that pyridine may be a weak inducer of α2μ-globulin in F344/N male rats, based on the observation of statistically significant increased incidence in granular casts and hyaline degeneration in the 1000 ppm pyridine-treated rats along with higher staining intensity for α2μ-globulin in the kidney tissues from F344/N male rats exposed to 1000 ppm pyridine (Ref. 17).

Using a weight-of-evidence analysis, we concluded that pyridine is unlikely to induce tumors in humans at its current exposure level as a synthetic flavoring substance and adjuvant in foods based on the following: (1) Pyridine is non-genotoxic; (2) renal tubule neoplasms likely involve multiple MOAs that may include α2μ-globulin nephropathy and CPN, which are not relevant to humans. These postulated mechanisms, specifically α2μ-globulin nephropathy, are species- and sex-specific; (3) B6C3F1 mice are prone to spontaneous hepatocellular adenomas, carcinomas, and hepatoblastomas with high background incidence; and (4) active metabolites of pyridine differ across species and appear to be dose-dependent.

Further, there is a large MOE (3.7×10^5) between the estimated dietary exposure of pyridine as a synthetic flavoring substance intentionally added to food (0.038 μg/kg bw/d) compared to the highest dose of pyridine at which no treatment-related, statistically significant tumors were observed in the NTP studies (14,000 μg/kg bw/d (rats)) (Ref. 17). This large MOE further supports our conclusion that pyridine, when used as a flavoring substance, is unlikely to induce cancer in humans.

IV. Comments on the Notice of Petition

FDA received a number of comments in response to the notice of the petition. Most comments expressed general support for revocation of the regulations for the seven synthetic flavoring substances, without providing any additional information. Several comments expressed concern about the safety of these synthetic flavoring substances and asked that FDA ban them from foods; however, these comments did not provide any information to support their claim that the use of these additives is unsafe.

We summarize and respond to relevant portions of comments in this final rule. To make it easier to identify comments and FDA's responses to the comments, the word ''Comment'' will appear in parentheses 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 make it easier to identify a particular comment. 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.

A. Legal and Policy Issues

(Comment 1) One comment stated that these synthetic flavoring substances should not be revoked based on the Delaney Clause because ''. . . the Delaney Clause does not mandate that FDA flatly prohibit the use of the substance under any circumstances.'' The comment goes on to say that ''[t]he determination that a substance triggers the Delaney Clause is not the same as a determination that the substance is necessarily unsafe in food and that ''. . . an outright ban of any of the flavorings identified by the petitioner would require FDA to explain—in a rulemaking procedure—why the substance not only triggers the Delaney Clause but also why there are no circumstances under which the substance could otherwise be

considered safe for food use under specified conditions of use.'' Several comments stated that FDA should interpret the Delaney Clause in a manner similar to the approach used by FDA in its Constituents Policy (*i.e.,* FDA may determine that a food or color additive is ''safe'' if it contains a carcinogenic constituent but is not itself carcinogenic, see 47 FR 14464, April 2, 1982) for carcinogenic contaminants present in certain food additives.

(Response 1) We disagree. The language of the Delaney Clause is straightforward. For most food additives, FDA has discretion to review a number of factors to determine whether a food additive is safe (section 409(c)(5) of the FD&C Act). However, for food 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 food additive is not safe. Furthermore, as described above, courts have rejected the interpretations of the Delaney Clause suggested in the comments and have concluded that the Delaney Clause completely bans additives found to induce cancer in humans or animals. Thus, as a matter of law, FDA cannot find these synthetic flavoring substances to be safe.

(Comment 2) One comment said that the Delaney Clause applies only to food additives that induce cancer in test animals through a direct, genotoxic mechanism of carcinogenicity. The comment further stated that there are numerous examples of food ingredients that produce increased incidence of tumors in high dose rodent studies through a threshold secondary mechanism.

(Response 2) We disagree. The Delaney Clause does not differentiate between non-genotoxic and genotoxic carcinogens. Nor does it permit FDA to find a food additive safe for human consumption if the food additive has induced cancer in animal. The Delaney Clause is a strict legal standard that precludes FDA from using its expertise to evaluate a substance under its intended condition of use and its risk to public health.

(Comment 3) One comment stated that the petitioners call for a radical departure from long-established regulatory framework of FDA conducting its own comprehensive review of the scientific data that bear on the safety assessment. Further, the comment stated that the petitioners' approach is contrary to the statute and cannot be implemented without amendment of the law. The comment stated that if, contrary to the statute and long precedent, FDA believes it should delegate its authority to external organizations, it must consider such policy changes through notice-and-comment rulemaking. The comment also stated that while an FAP is the correct vehicle to appeal/amend a food additive regulation, it is not appropriate for FDA to consider, much less implement, ''radical new interpretations'' of the statute through a food additive petition.

(Response 3) FDA disagrees with this comment. FDA's regulations permit petitioning the agency to revoke a food additive regulation. In response to such a petition, FDA conducts its own review of scientific data that bear on the petition. FDA then takes action based on its own evaluation of the data in accordance with the FD&C Act and its implementing regulations. The Delaney Clause is in the FD&C Act and this rulemaking is in accordance with the language of the law and case law interpreting it.

B. Scientific Issues

(Comment 4) One comment included a lengthy discussion of relevant carcinogenicity and genotoxicity studies for each of the additives that are the subject of the petition and argued that none of the synthetic flavoring substances are direct carcinogens. Instead, the comment contended that tumors observed in the NTP studies were the result of secondary mechanisms and not direct, genotoxic effects.

(Response 4) Our review included an evaluation of all relevant carcinogenicity studies for each of the additives. The toxicology memoranda for each of the six synthetic flavoring substances and section III include a full discussion of the relevant studies and address each scientific point outlined in the comment.

(Comment 5) Several comments believed that FDA should not base its safety decision solely on classifications by NTP or IARC and that any decision should be based on an independent FDA assessment. Another comment stated that FDA must consider new studies since the NTP and IARC reviews were completed.

(Response 5) FDA agrees with the comments and has conducted its own evaluation of available relevant data to reach its conclusions on each synthetic flavoring substance, and did not solely rely on NTP and IARC classifications as the basis for our decision.

(Comment 6) One comment noted that IARC is not subject to U.S. law and relying on its conclusions is inappropriate and legally vulnerable for FDA. Another comment noted that IARC warns that its monographs are not the basis for governmental action, pointing out that the preamble to IARC monographs is clear that they are a starting place for government agencies, not a basis for regulation.

(Response 6) We agree that relying solely on IARC conclusions would not be appropriate in making a decision on the petition, and, as such, FDA has conducted its own comprehensive carcinogenicity evaluation of the flavoring substances using all available relevant information.

(Comment 7) One comment stated that the international health and safety community has moved away from rote reliance on IARC and NTP. The comment further said that the NTP and IARC classifications do not make those substances carcinogens under the Occupational Safety and Health Administration (OSHA) Hazard Communication Standard and that these reviews are not viewed as weight-of-evidence conclusions by international authorities; therefore, it would be incongruent for FDA to view them in this manner. The comment cited an action in 2012, where OSHA reversed three decades of automatically requiring employers to classify a substance as a carcinogen based on an NTP or IARC classification.

(Response 7) FDA acknowledges that the NTP studies are designed for hazard identification and not for assessing the human carcinogenicity risk of chemicals under specific conditions of use; however, FDA must evaluate the results from the NTP studies and other available information within the context of the FD&C Act, including the Delaney Clause.

(Comment 8) Some comments expressed concern that compliance and enforcement of a zero tolerance policy is not possible and that a zero tolerance policy is not feasible for naturally occurring substances.

(Response 8) FDA has not addressed the request for FDA to establish zero tolerances for the food additives that are the subject of this petition because such a request is not the proper subject of a food additive petition, and because the petitioners have indicated that they are abandoning that claim.

(Comment 9) Several comments expressed concern over the use of these substances in food packaging applications.

(Response 9) Benzophenone is the only synthetic flavoring substance that is the subject of this petition that also is approved as a food additive for use in food packaging (§ 177.2600(c)(4)(iv) diphenylketone). As explained earlier, we are repealing the regulation for the

use of this substance as a plasticizer in food packaging based on results of the NTP studies.

(Comment 10) One comment said that the use of ethyl acrylate should not be revoked, because the studies used to assess carcinogenicity were not appropriate and noted that NTP has removed it from its list of human carcinogens.

(Response 10) FDA acknowledges that NTP has removed ethyl acrylate from its list of human carcinogens; however, the flavoring substance induced cancer in animals under the conditions of the 2-year NTP carcinogenicity studies. As such, we are required under the Delaney Clause to deem the additive to be unsafe as a matter of law. (See Section III.B, Ethyl Acrylate.)

(Comment 11) One comment submitted on behalf of several industry interests supported removal of styrene from § 172.515 based solely on abandonment and subsequently submitted a petition (FAP 6A4817 (81 FR 38984)) providing data to support their claim.

(Response 11) FDA is responding to this comment as part of our response to FAP 6A4817, which is published elsewhere in this edition of the **FEDERAL REGISTER**.

(Comment 12) One comment stated that the petitioner should follow the National Environmental Policy Act and submit an environmental assessment but did not provide any supporting data.

(Response 12) FDA disagrees. As discussed in section VII, we have determined that the action we are taking on the petition does not have a significant effect on the human environment and neither an environmental assessment nor an environmental impact statement is required.

V. 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 synthetic benzophenone, ethyl acrylate, methyl eugenol, myrcene, pulegone, and pyridine have been shown to cause cancer in animals. Despite FDA's scientific analysis and determination that these substances do not pose a risk to public health under the conditions of their intended use, under the Delaney Clause this finding of carcinogenicity renders the additives ''unsafe'' as a matter of law and FDA is compelled to amend the authorizations for these substances as food additives to no longer provide for the use of these synthetic flavoring substances. Additionally, because of evidence that benzophenone causes cancer in animals, FDA also is amending the food additive regulations to no longer provide for the use of benzophenone as a plasticizer in rubber articles intended for repeated use in contact with food. Therefore, we are amending parts 172 and 177 as set forth in this document. Upon the publication, these food additive uses are no longer authorized.

FDA realizes that the food industry needs sufficient time to identify suitable replacement ingredients for these synthetic flavoring substances and reformulate products and for these products to work their way through distribution. Therefore, FDA intends to not enforce applicable requirements of the final rule with regard to food products manufactured (domestically and internationally) prior to October 9, 2020 that contain one or more of these six synthetic flavoring substances, to provide an opportunity for companies to reformulate products prior to enforcing the requirements of this final rule.

VI. Public Disclosure

In accordance with § 171.1(h) (21 CFR 171.1(h)), 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 § 171.1(h), we will delete from the documents any materials that are not available for public disclosure.

VII. Analysis of Environmental Impacts

As stated in the January 4, 2016, **Federal Register** notice of petition for FAP 5A4810 (81 FR 42), the petitioners claimed a categorical exclusion from preparing an environmental assessment or environmental impact statement under 21 CFR 25.32(m). We have determined that the categorical exclusion under § 25.32(m) for actions to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics is warranted. We have determined under § 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.

VIII. Paperwork Reduction Act of 1995

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

IX. Objections

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.*

X. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**), under Docket No. FDA–2015–F–4317, 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 display; they are available as published articles and books.

1. Bevan, R.J. (2017). ''Threshold and Non-Threshold Chemical Carcinogens: A survey of the Present Regulatory Landscape.'' *Regulatory Toxicology and Pharmacology,* 88, 291–302.
2. JECFA (2006). ''The Formulation of Advice on Compounds That are Both Genotoxic and Carcinogenic.'' WHO Food Additives Series No. 55, Annex 4.
3. Barlow, S. et al. (2006). ''Risk Assessment of Substances That are Both Genotoxic and Carcinogenic: Report of an International Conference organized by EFSA and WHO with Support of ILSI Europe.'' *Food and Chemical Toxicology,* 44, 1636–1650.
4. Flavor and Extract Manufacturers Association Transmittal Letter to Szabina Stice (FDA, CFSAN), April 27, 2018.*
5. FDA Memorandum from D. Folmer, CFSAN Chemistry Review Group,

Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 24, 2016.*
6. FDA Memorandum from D. Folmer, CFSAN Chemistry Review Group, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 20, 2018.*
7. Food and Agriculture Organization of the United Nations and the World Health Organization. Principles and Methods for the Risk Assessment of Chemicals in Food. 2009. Available at *http://www.inchem.org/documents/ehc/ehc/ehc240_index.htm.* (Last accessed September 12, 2017.)
8. Flavor and Extract Manufacturers Association Letter to Judith Kidwell (FDA, CFSAN), April 11, 2016.*
9. FDA Memorandum from S. Thurmond, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 21, 2018. *
10. Boobis, A.R. et al. (2006). ''IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans.'' *Critical Reviews in Toxicology,* 36:10, 781–792.
11. FDA Memorandum from S. Thurmond, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 21, 2018.*
12. National Toxicology Program. Report on Carcinogens Background Document for Ethyl Acrylate. December 2–3, 1998.
13. FDA Memorandum from J. Zang, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 21, 2018.*
14. FDA Memorandum from A. Khan, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 21, 2018.*
15. FDA Memorandum from N. Anyangwe, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 21, 2018.*
16. Da Rocha, M.S., Dodmane, P.R., Arnold, L.L., et al. (2012). ''Mode of Action of Pulegone on the Urinary Bladder of F344 Rats.'' *Toxicological Sciences,* kfs035.
17. FDA Memorandum from T. Tyler, CFSAN Toxicology Team, Division of Petition Review, to J. Kidwell, Regulatory Group I, Division of Petition Review, June 27, 2018.*

List of Subjects

21 CFR Part 172

Food additives, Reporting and recordkeeping requirements.

21 CFR Part 177

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 172 and 177 are amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

■ 1. The authority citation for part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

§ 172.515 [Amended]

■ 2. Amend § 172.515(b) by removing the entries for ''benzophenone; diphenylketone,'' ''ethyl acrylate,'' ''eugenyl methyl ether; 4-allylveratrole; methyl eugenol,'' ''myrcene; 7-methyl-3-methylene-1,6-octadiene,'' ''pulegone; *p*-menth-4(8)-en-3-one,'' and ''pyridine.''

PART 177—INDIRECT FOOD ADDITIVES: POLYMERS

■ 3. The authority citation for part 177 continues to read as follows:

Authority: 21 U.S.C. 321, 342, 348, 379e.

§ 177.2600 [Amended]

■ 4. In § 177.2600(c)(4)(iv), remove the entry for ''diphenyl ketone.''

Dated: October 2, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–21807 Filed 10–5–18; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 165

[Docket Number USCG–2018–0682]

RIN 1625–AA00

Safety Zone; North Hero-Grand Isle Bridge, Lake Champlain, VT

AGENCY: Coast Guard, DHS.

ACTION: Temporary interim rule and request for comments.

SUMMARY: The Coast Guard is establishing a temporary safety zone for the navigable waters within a 50 yard radius from the center of the North Hero-Grand Isle Bridge, on Lake Champlain, VT. The safety zone is necessary to protect personnel, vessels, and marine environment from potential hazards created by the demolition, subsequent removal, and replacement of the North Hero-Grand Isle Bridge. When enforced, this regulation prohibits entry of vessels or persons into the safety zone unless authorized by the Captain of the Port Northern New England or a designated representative.

DATES: This rule is effective without actual notice from October 9, 2018 through September 1, 2022. For purposes of enforcement, actual notice will be used from October 1, 2018 through October 9, 2018.

Comments and related material must be received by the Coast Guard on or before January 7, 2019.

ADDRESSES: To view documents mentioned in this preamble as being available in the docket, go to *http://www.regulations.gov,* type USCG–2018–0682 in the ''SEARCH'' box and click ''SEARCH.'' Click on Open Docket Folder on the line associated with this rule. You may submit comments identified by docket number USCG–2018–0575 using the Federal eRulemaking Portal at *http://www.regulations.gov. See the* ''*Public Participation and Request for Comments*'' *portion for further instructions on submitting comments.*

FOR FURTHER INFORMATION CONTACT: If you have questions on this rule, call or email LT Matthew Odom, Waterways Management Division, U.S. Coast Guard Sector Northern New England, telephone 207–347–5015, email *Matthew.T.Odom@uscg.mil.*

SUPPLEMENTARY INFORMATION:

I. Table of Abbreviations

CFR Code of Federal Regulations
COTP Captain of the Port
DHS Department of Homeland Security
FR Federal Register
TIR Temporary Interim Rule
NPRM Notice of proposed rulemaking
§ Section
U.S.C. United States Code

II. Background Information and Regulatory History

On July 5, 2018, Sector Northern New England was made aware by Cianbro Corporation through email, of the North Hero-Grand Isle Bridge replacement project, which will be replacing Bridge 8 on US 2 over Lake Champlain which connects the towns of North Hero Island and Grand Isle in Vermont. The COTP Northern New England has determined that the potential hazards associated with the bridge replacement project will be a safety concern for anyone within the work area.

The Coast Guard is publishing this rule to be effective, and enforceable, through September 1, 2022, in case the project is delayed due to unforeseen circumstances. During this project, removal and replacement of the bridge will take place. No vessel or person will be permitted to enter the safety zone without obtaining permission from the