The Proposal

The FAA is proposing an amendment to Title 14, Code of Federal Regulations (14 CFR) part 71 by establishing Class E airspace extending upward from 700 feet above the surface within a 6.4-mile radius of Glen Ullin Regional Airport, Glen Ullin, ND, to accommodate new standard instrument approach procedures developed for the airport. This action would enhance safety and the management of IFR operations at the airport.

Class E airspace designations are published in paragraph 6005 of FAA Order 7400.11B, dated August 3, 2017, and effective September 15, 2017, which is incorporated by reference in 14 CFR 71.1. The Class E airspace designation listed in this document will be published subsequently in the Order.

Regulatory Notices and Analyses

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current, is non-controversial and unlikely to result in adverse or negative comments. It, therefore: (1) Is not a ''significant regulatory action'' under Executive Order 12866; (2) is not a ''significant rule'' under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this proposed rule, when promulgated, would not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

Environmental Review

This proposal will be subject to an environmental analysis in accordance with FAA Order 1050.1F, ''Environmental Impacts: Policies and Procedures'' prior to any FAA final regulatory action.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

The Proposed Amendment

Accordingly, pursuant to the authority delegated to me, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(f), 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of FAA Order 7400.11B, Airspace Designations and Reporting Points, dated August 3, 2017, and effective September 15, 2017, is amended as follows:

Paragraph 6005 Class E Airspace Areas Extending Upward From 700 Feet or More Above the Surface of the Earth.

* * * * *

AGL WI E5 Glen Ullin, ND [New]

Glen Ullin Regional Airport, ND
(Lat. 46°48′52″ N, long. 101°51′55″ W)

That airspace extending upward from 700 feet above the surface within a 6.4-mile radius of Glen Ullin Regional Airport.

Issued in Fort Worth, Texas, on May 9, 2018.

Walter Tweedy,

Acting Manager, Operations Support Group, ATO Central Service Center.

[FR Doc. 2018–10654 Filed 5–18–18; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. FDA–2015–F–3663]

Grocery Manufacturers Association; Denial of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification; denial of petition.

SUMMARY: The Food and Drug Administration (FDA or we) is denying a food additive petition (FAP 5A4811), submitted by the Grocery Manufacturers Association (GMA), requesting that the food additive regulations be amended to provide for the safe use of partially hydrogenated vegetable oils (PHOs) in certain food applications. We are denying the petition because we have determined that the petitioner did not provide sufficient information for us to conclude that the requested uses of PHOs are safe. To allow the food industry sufficient time to identify suitable replacement substances for the petitioned uses of PHOs, elsewhere in this issue of the **Federal Register** we have extended the compliance date for certain uses of PHOs, including the conditions of use covered by the FAP.

DATES: This document is applicable May 21, 2018. Submit either electronic or written objections and requests for a hearing on the document by June 20, 2018. Late, untimely objections will not be considered. See section VIII for further information on the filing of objections.

ADDRESSES: You may submit objections and requests for a hearing as follows.

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'').
- The *https://www.regulations.gov* electronic filing system will accept objections until midnight Eastern Time at the end of June 20, 2018.

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.''
- 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 June 20, 2018.

Instructions: All submissions received must include the Docket No. FDA–2015–F–3663 for ''Grocery Manufacturers Association; Denial of Food Additive Petition.'' 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.'' The Agency will review this copy, including the claimed confidential information, in its 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: Ellen Anderson, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740–3835, 240–402–1309.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a document published in the **Federal Register** on October 28, 2015 (80 FR 65978), we announced that we filed FAP 5A4811 (''petition'') submitted by the Grocery Manufacturers Association, 1350 I St. NW, Suite 300, Washington, DC 20005 (''petitioner''). The petitioner requested that we amend the food additive regulations in 21 CFR part 172 *Food Additives Permitted for Direct Addition to Food for Human Consumption* to provide for the safe use of partially hydrogenated vegetable oils (PHOs) in the following food applications at specified maximum use levels: as a carrier or component thereof for flavors or flavorings, as a diluent or component thereof for color additives, as an incidental additive or processing aid, and as a direct additive in approximately 60 food categories. The petition was submitted in response to FDA's declaratory order issued on June 17, 2015 (80 FR 34650), announcing our final determination that there is no longer a consensus among qualified experts that PHOs are generally recognized as safe for any use in human food. In the declaratory order, we invited submission of food additive petitions with scientific evidence for one or more specific uses of PHOs for which the petitioner believes that safe conditions of use may be prescribed (as further discussed in section II).

FAP 5A4811 was submitted by GMA to FDA on June 11, 2015. During our initial review, we determined that the petition did not contain an environmental assessment as required under 21 CFR 25.15(a); therefore, we informed GMA that their petition did not meet the minimum requirements for filing in accordance with 21 CFR 171.1(c). On September 18, 2015, GMA resubmitted a complete FAP 5A4811, which we subsequently filed on October 1, 2015. During our initial review of FAP 5A4811, we identified several deficiencies that required resolution by GMA for us to continue with our review. We issued a letter to GMA on March 21, 2016, explaining the additional information required to resolve the petition's deficiencies. On May 5, 2016, GMA submitted a partial response to the deficiencies. The petition was then placed in abeyance by FDA, consistent with our procedures for food additive petitions.[1] The petitioner and FDA met several times in the months following to discuss the deficiencies.

On March 7, 2017, the petitioner submitted a substantive amendment to FAP 5A4811 that addressed the deficiencies identified by FDA. In accordance with 21 CFR 171.6, the petition was assigned a new filing date of March 7, 2017. The amended petition contained significant revisions to the proposed uses, exposure estimate, and safety assessment of PHOs. The revised petitioned uses of PHOs were limited to the following: (1) As a solvent or carrier for flavoring agents, flavor enhancers, and coloring agents; (2) as a processing aid, and (3) as a pan release agent for baked goods. Based on the revisions, the petitioner asserted that the amended uses of PHOs would present a de minimis increase in risk (in other words, a negligible increase in risk) and, therefore, are safe under the conditions of intended use. References to the ''petition'' henceforth in this document will denote the amended petition received on March 7, 2017.

II. Background

A. Statutory and Regulatory Requirements Regarding Food Additives

The Federal Food, Drug, and Cosmetic Act (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, if such substance is not generally recognized by experts as safe under the conditions of its intended use (section 201(s) of the FD&C Act (21 U.S.C. 321(s))). Food additives are deemed unsafe and prohibited except to the extent that FDA approves their use (sections 301(a) and (k) (21 U.S.C. 331(a) and (k)) and 409(a) (21 U.S.C. 348(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 (section 409(b)(1) of the FD&C Act). When FDA concludes that a proposed use of a food additive is safe, we issue a regulation authorizing a specific use of the substance.

B. Relevant Regulatory History of PHOs

On November 8, 2013, FDA issued a document (the tentative determination,

[1] Abeyance is an administrative category of petitions that are filed but non-active because of deficiencies that were identified during FDA's review. A petition remains in abeyance until either the petitioner provides FDA with the required information, requests a final decision based on the data currently in the petition, or requests withdrawal of the petition.

78 FR 67169), announcing our tentative determination that PHOs are no longer generally recognized as safe (GRAS) under any condition of use in food and therefore are food additives subject to section 409 of the FD&C Act. Because PHOs are the primary dietary source of industrially-produced *trans* fatty acids (IP–TFA), FDA's evaluation of the GRAS status of PHOs centered on the *trans* fatty acid (TFA, also referred to as ''*trans* fat'') component of these fats and oils. The tentative determination cited current scientific evidence of significant human health risks, namely an increased risk in coronary heart disease (CHD), associated with the consumption of IP–TFA (78 FR 67169 at 67172). The scientific evidence included results from controlled feeding studies on *trans* fatty acid consumption in humans, findings from long-term prospective epidemiological studies, and the opinions of expert panels that there is no threshold intake level for IP–TFA that would not increase an individual's risk of CHD (78 FR 67169 at 67172). Based on the evidence outlined in the tentative determination, we determined that there is no longer a consensus among qualified experts that PHOs are safe for human consumption (*i.e.,* PHOs do not meet the GRAS criteria.) The tentative determination also requested interested parties to submit comments and additional scientific data related to our tentative determination that PHOs are no longer GRAS (78 FR 67169 at 67174).

We received over 6000 comments in response to the tentative determination. We reviewed the comments before issuing our final determination as a declaratory order published on June 17, 2015 (the declaratory order, 80 FR 34650). The declaratory order included four major provisions: (1) PHOs are not GRAS for any use in human food; (2) for the purposes of the declaratory order, FDA defined PHOs as those fats and oils that have been hydrogenated, but not to complete or near complete saturation, and with an iodine value greater than 4 as determined by an appropriate method; (3) any interested party may seek food additive approval for one or more specific uses of PHOs with data demonstrating a reasonable certainty of no harm of the proposed use(s); and (4) FDA established a compliance date of June 18, 2018 (80 FR 34650 at 34651).

In our declaratory order finding that PHOs are no longer GRAS for any use in human food, we acknowledged that scientific knowledge advances and evolves over time. The declaratory order invited submission of scientific evidence as part of food additive petitions under section 409 of the FD&C Act for one or more specific uses of PHOs for which industry or other interested individuals believe that safe conditions of use may be prescribed. We also established a three-year delayed compliance date (compliance required no later than June 18, 2018) to provide time for submission and review and, if applicable requirements are met, approval of food additive petitions for uses of PHOs (80 FR 34650 at 34668).

III. Evaluation of Safety

A food additive cannot be approved for use unless the data presented to us 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 us 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, taking into account any chemically or pharmacologically related substances in the diet; and (3) safety factors generally recognized by experts as appropriate for the use of animal experimentation data (section 409(c)(5) of the FD&C Act). Our 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) (21 CFR 170.3(i))).

FAP 5A4811 is not a typical food additive petition in that it is requesting food additive approval for existing uses of PHOs that industry, independent of FDA, had concluded were GRAS, but FDA subsequently determined such uses are not GRAS. Most food additive petitions seek premarket approval for new uses of food additives. Additionally, the approach that we normally use to evaluate safety of a direct food additive is not applicable for assessing the safety of IP–TFA in PHOs. Food additives are typically evaluated based on toxicological studies in animals, as described in our guidance, *Toxicological Principles for the Safety of Assessment of Food Ingredients* (also known as Redbook 2000).[2] However, key scientific evidence for the association of *trans* fat and CHD is based on human studies, including controlled feeding trials of *trans* fat intake and blood cholesterol levels in humans and long-term, prospective observational studies of *trans* fat intake and CHD risk in human populations (Ref. 1).

To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, we typically consider the projected human dietary exposure to the additive, the additive's toxicological data provided by the petitioner, and other relevant information (such as published literature) available to us. FDA scientists use these toxicological data (usually derived from animal and in vitro studies) to determine a no-observed effect level or a no-observed-adverse-effect-level, apply an appropriate safety factor to account for differences between animals and humans and differences in sensitivity among humans, and calculate the acceptable daily intake (ADI) for the food additive. The ADI is usually expressed in milligrams of food additive per kilogram body weight of humans. We compare an individual's estimated daily intake (EDI) of the additive from all food sources to the ADI established by toxicological data. The EDI is determined based on the amount of the additive proposed for use in particular foods and the amount of those foods consumed containing the additive, and on the amount of the additive from all other dietary sources. We typically use the EDI for the 90th percentile consumer of a food additive as a measure of high chronic dietary exposure. A food additive is generally considered safe for its intended uses if the EDI of the additive is less than the ADI. This approach assumes that a physiological threshold may exist below which exposure to an additive will not cause harm. In the case of PHOs, which contribute IP–TFA to the diet, the main toxicological data available to assess safety consists of controlled feeding trials and prospective observational studies in humans where the adverse health outcomes associated with the additive are increased CHD risk and other non-cancer risks (*e.g.,* stroke). To receive approval for the petitioned uses of PHOs, the petitioner has the responsibility to provide scientific evidence that establishes that the intended uses of PHOs are safe, including the expected dietary exposure to *trans* fat resulting from the intended uses of PHOs.

Our declaratory order references three safety memoranda prepared by FDA that document our review of the available scientific evidence regarding human health effects of *trans* fat, focusing on the adverse effects of *trans* fat on risk of CHD (Refs. 2–4). In addition, we previously reviewed the health effects of IP–TFA and PHOs in support of our tentative determination that PHOs are not GRAS in food (78 FR 67169) and in

[2] Redbook 2000 is available at *https://www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf.*

1999 and 2003 in support of our proposed and final rules requiring declaration of *trans* fat in nutrition labeling of food (64 FR 62746 and 68 FR 41434). The safety reviews for the declaratory order, together with the previous safety reviews of IP–TFA and PHOs, provide important background scientific information for our review of FAP 5A4811.

The petition contains a review of recent scientific literature and expert opinions on *trans* fat consumption. GMA asserted that this information supports the following three conclusions, which are their reasons why they believe the petitioned uses of PHOs are safe:

1. ''The conservatively estimated probability of coronary heart disease risk falls below the probable *de minimis* non-cancer risk range.'' [3]

2. ''iTFA [4] exposure from the petitioned uses of PHOs (*i.e.,* 0.05%en [total energy intake per day]) is well below exposure levels in controlled feeding trials, and effects at these low iTFA exposures levels cannot be empirically established based on the currently available evidence.''

3. ''The incremental increase in iTFA intake of 0.05%en from the petitioned uses of PHOs is infinitesimally small and negligible in comparison to existing background dietary TFA exposure from intrinsic sources.''

(Petition, pp. 116–119)

In this petition denial, we discuss our evaluation of the petitioner's request and supporting information in section IV organized according to the following headings: A. Chemical Identity, Intended Technical Effects, and Petitioned Uses of PHOs; B. Estimated Exposure to *Trans* Fat; C. Recent Scientific Literature and Expert Opinions on *Trans* Fat Consumption; D. Recent Threshold Dose-Response Research; and E. Risk Estimates and Safety Arguments. Each of these sections provides a summary of the information provided by the petitioner followed by our evaluation of that information, prefaced with ''*FDA Assessment.*'' Additional information regarding our evaluation of the petition can be found in our three review memoranda (Refs. 5–7).

[3] As discussed in section E, the petitioner calculates what it considers to be de minimis risks for non-cancer health outcomes.

[4] The petitioner uses the abbreviation iTFA to refer to industrially-produced TFA in the petition.

IV. FDA's Review of FAP 5A4811

A. Chemical Identity, Intended Technical Effects, and Petitioned Uses of PHOs

The PHOs that are the subject of FAP 5A4811 are made from the following vegetable oils: Soy, cottonseed, coconut, canola, palm, palm kernel, and sunflower oils, or blends of these oils, and consist of up to 60 percent *trans* fatty acids. As discussed in section I, GMA requested approval of three uses of PHOs, which are as follows:

- PHO, or a blend of PHOs, used as a solvent or carrier, or a component thereof, for flavoring agents, flavor enhancers, and coloring agents intended for food use, provided the PHOs in the solvent or carrier contribute no more than 150 parts per million (ppm) (150 milligrams per kilogram (mg/kg)) IP–TFA to the finished food as consumed;
- PHO, or a blend of PHOs, used as a processing aid, or a component thereof, provided the PHOs in the processing aid contribute no more than 50 ppm (50 mg/kg) IP–TFA to the finished food as consumed;
- PHO, or a blend of PHOs, used as a pan release agent for baked goods at levels up to 0.2 grams/100 grams (0.2 g/100 g) in pan release spray oils, provided the PHO contributes no more than 0.14 g IP–TFA/100 g spray oil.

These proposed uses excluded dietary supplements. The physical and technical effects of the petitioned uses of PHOs were specified as: Release agents, either alone or in combination with other components (§ 170.3(o)(18)); processing aids or components thereof (§ 170.3(o)(24)); and as solvents, carriers and vehicles for fat soluble coloring agents, flavoring agents, and flavor enhancers (§ 170.3(o)(27)).

FDA Assessment

To better understand how PHOs would be used as processing aids, we requested that the petitioner provide specific examples. In an email dated May 15, 2017, the petitioner provided several examples of how PHOs may be used as processing aids. Many of the petitioner's examples involved the use of PHOs as a topical coating to prevent rancidity (*e.g.,* PHO-coated almond slices or candy pieces used as ingredients in cookies). We view this use of PHOs as having an ongoing technical effect in food (*e.g.,* to prevent rancidity and oxidation) and, therefore, we do not agree that this use would be considered a processing aid in accordance with §§ 170.3(o)(24) and 101.100(a)(3)(ii) (21 CFR 101.100(a)(3)(ii)). Because we are denying this petition, we did not need to resolve this issue regarding characterization of the technical or functional effect of these additives.

B. Estimated Exposure to Trans Fat

The petitioner provided exposure estimates for TFA from the petitioned uses of PHOs and from intrinsic (*i.e.,* naturally-occurring) sources such as dairy and meat from ruminant animals. To estimate exposure, the petitioner used food disappearance data from 2014 compiled by the U.S. Department of Agriculture (USDA) Economic Research Service, food consumption data from either the 2007–2010 or 2009–2012 National Health and Nutrition Examination Surveys (NHANES), and the intrinsic concentrations of TFA in the USDA National Nutrient Database for Standard Reference Release 27. The petitioner estimated the exposure to naturally-occurring TFA from intrinsic sources for the U.S. population (aged 2 years or more) to be 1.04 grams/person/day (g/p/d) at the mean and 1.91 g/p/d at the 90th percentile. If expressed as a percentage of total energy intake per day (%en), based on a 2000 calorie daily diet, the exposure to TFA from intrinsic sources would be 0.46%en at the mean and 0.75%en at the 90th percentile for the U.S population. The petitioner estimated the cumulative exposure to IP–TFA from all petitioned uses of PHOs in foods for the U.S. population aged 2 years or more to be 0.121 g/p/d (0.05%en) at the mean and 0.122 g/p/d (0.05%en) at the 90th percentile.

FDA Assessment

FDA agrees with the petitioner's estimated exposure to TFA from intrinsic sources, and we have no concerns regarding the general methodology used by the petitioner to estimate exposure to IP–TFA from the petitioned uses of PHOs. However, we believe the petitioner likely underestimated exposure to IP–TFA from the petitioned uses of PHOs for various reasons, such as their determination that 43 percent of the U.S. diet consists of processed foods, which we believe is too low, and not including all relevant NHANES food codes in their exposure estimate (Ref. 5). Although the petitioner's exposure estimate could be refined, we consider it sufficient for approximating exposure from the petitioned uses of PHOs.

C. Recent Scientific Literature and Expert Opinions on Trans Fat Consumption

FAP 5A4811 included sections on dietary guidelines and expert panel opinions pertaining to *trans* fat consumption. In addition, the petition

presented a summary of studies assessing the effects of dietary TFA on intermediate biomarkers such as low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and other emerging biomarkers of CHD risk, and the association of dietary TFA intake with risk of CHD and risk of adverse health outcomes other than CHD (*e.g.,* stroke, metabolic syndrome). Controlled feeding trials, prospective observational studies, and meta-analyses of these studies were included in the petitioner's scientific literature review.

FDA Assessment

As discussed in our review memorandum (Ref. 7), we found that the petitioner provided incomplete information on certain topics or misinterpreted some scientific conclusions.

1. Dietary Guidelines and Expert Panel Reviews

The petition discussed the major expert panel reports on the health effects of *trans* fat consumption from the U.S., Australia, Canada, the United Kingdom, the World Health Organization (WHO), the Food and Agriculture Organization, and the European Food Safety Authority. We note that while the petition provided a generally accurate summary of these expert reports, some important information was missing or understated. For example, the petition omits the expert opinions on the role of HDL–C as a biomarker for CHD. The petition also omits that, in addition to the Institute of Medicine's 2005 report (Ref. 8), many other expert panels have concluded that TFA has a progressive and linear adverse effect on blood lipids and associated CHD risk. Furthermore, the petition understated the recommendation from several expert panels that *trans* fat intake should be kept as low as possible by specifically limiting intake of IP–TFA from PHOs.

2. Effect of Changes In *Trans* Fat Intake on LDL–C and HDL–C

The petition identified five meta-analysis studies (which are combined analyses of multiple feeding trials) that quantified the effect of changes in *trans* fat intake on LDL–C and HDL–C in the blood of human test subjects. The petition's summary of these studies was appropriate; however, we note that two available meta-analyses studies were not included in the petition's discussion: Zock and co-workers (Refs. 9–11) and Brouwer (Ref. 12). In particular, the 2016 meta-analysis by Brouwer was an important study, commissioned by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health, that affirmed the linear, progressive effect of *trans* fat intake on blood cholesterol levels (Ref. 12).

The petition mentioned another meta-analysis of newer studies conducted by Hafekost et al. (2015) which reported no significant effect on LDL–C from a 1%en TFA intake (including both naturally-occurring TFA and IP–TFA) in exchange for *cis*-monounsaturated fatty acids (*cis*-MUFA) (Ref. 13). The petition claimed that these results support the potential for a threshold *trans* fat intake below which no significant effect on blood lipids is observed. However, we disagree with the petitioner's interpretation of this study's conclusions (Ref. 7). We note that the criteria for inclusion of feeding trials in this meta-analysis were not rigorous. In several of the included studies, the diets were not fully controlled. We also note that Hafekost et al. did not conclude that their results supported the potential for a safe threshold intake level of TFA. Rather, the authors stated, ''An increase in LDL was consistent with the results of Brouwer et al., who identified a significant increase in LDL cholesterol with a percent increase in the intake of industrial TFA.'' Furthermore, Hafekost et al. conducted an additional analysis, including the earlier Brouwer et al. meta-analysis results together with their analysis of newer studies alone. The petition did not discuss these additional analyses. The combined results for the newer studies alone, together with the earlier meta-analysis, showed a statistically significant increase in LDL–C due to an increase of 1%en intake from TFA. In their overall summary, Hafekost et al. stated, ''The results of the current review are consistent with previous evidence which indicates a detrimental effect of consumption of TFA on changes in LDL and HDL blood cholesterol'' (Ref. 13).

Regarding HDL–C and CHD risk, the petition underemphasized the impact of *trans* fat intake on HDL–C. We note that the observed decrease in HDL–C due to TFA intake is consistently reported across the existing body of TFA research and that HDL–C has been recognized as a major risk factor for CHD (Ref. 7).

3. Prospective Observational Studies

The petition reviewed the results of prospective observational studies that estimate the association of long-term, habitual TFA intake with CHD risk in large, free-living populations. The petition reviewed five meta-analysis studies (that provided combined analyses of several individual prospective observational studies). The petition stated that the results of a recent meta-analysis by de Souza et al. in 2015 (Ref. 14) were consistent with previous meta-analyses in finding a statistically significant increased risk of CHD when comparing high to low TFA intake. Regarding individual prospective observational studies, the petition stated that, ''The results from these studies, while not able to demonstrate causality, provide supporting evidence that, although a relationship between increased CHD risk and high levels of TFA intake exists, this observed relationship is largely based on comparisons of differences in TFA intake above 1%en and has not been established at lower levels of intake.''

We note that the overall results of the meta-analyses and recently published prospective observational studies were generally summarized accurately in the petition. However, the petition tended to understate the strength of the evidence from the observational studies reviewed. In particular, the meta-analysis by de Souza et al., a rigorously conducted study commissioned by WHO NUGAG, stated that the ''positive associations between *trans* fat intake and CHD and CHD mortality'' were ''reliable and strong'' and provided supplementary analyses supporting a progressive and linear association of TFA intake and CHD risk (Ref. 14). Additionally, recently published studies by Li et al. in 2015 (Ref. 15) and Wang et al. in 2016 (Ref. 16), with long-term followup and increased statistical power, show significant increases in CHD or cardiovascular disease (CVD) risk at lower increments of TFA intake than the 1%en stated by the petitioner.

4. Other Health Outcomes

The petitioner concluded, after reviewing recent scientific literature, that there is limited, inconsistent, and/or weak evidence for any effects of *trans* fat intake on other health outcomes including stroke, all-cause mortality, cancer, and metabolic syndrome. We do not agree with the petitioner's conclusion, in particular regarding stroke. In support of the declaratory order, we reviewed several well-conducted studies that provided a reasonable basis to conclude that TFA intake is associated with an increased risk of ischemic stroke (a blockage of blood flow to the brain) (Ref. 2). Furthermore, in our review memorandum for this petition, we described more recent studies that provide additional evidence supporting the association of TFA with stroke, as well as total mortality and elements of metabolic syndrome (Ref. 7).

D. Recent Threshold Dose-Response Research

The petition acknowledged that all five of the aforementioned meta-analyses (see section C) relied on a linear, no-threshold dose-response relationship between TFA intake and blood levels of LDL–C and HDL–C, which assumes any amount of TFA greater than 0%en causes adverse effects on blood cholesterol levels. The petition stated, ''Recent research suggests that a non-threshold linear dose-response model overlooks the complexities of the physiological effects of macronutrients and other contributing factors to LDL–C levels besides TFAs.'' In particular, the petition cited two recent articles to support the claims that a linear dose-response model is inappropriate for assessing the effects of TFA consumption on blood lipids, and that a threshold level of *trans* fat intake exists (Refs. 17 and 18). In the first publication, Reichard and Haber (Ref. 17) presented and evaluated a hypothesis for the biological mode of action (MOA) for the effect of TFA on LDL–C based on animal studies. According to the petition, ''. . . the authors concluded the key events in the MOA are the increased production of very low density-lipoprotein (VLDL) and decreased LDL-clearance due to a reduction in the LDL–C mediated receptor activity.'' The authors further concluded the effect of TFA on LDL–C is non-linear and there is evidence that either a threshold exists or the dose-response slope is very shallow at low dose levels (Ref. 17).

In the second article, Allen et al. (Ref. 18) conducted a meta-regression study of human controlled feeding trials, that considered both linear and nonlinear dose-response models to assess the effect of IP–TFA intake on LDL–C and determine which shape fit best with the MOA proposed by Reichard and Haber based on animal studies. (In this case, the meta-regression is a meta-analysis that focuses on dose-response relationships.) The Allen et al. meta-regression used an evidence map to identify additional experimental data for the effect of IP–TFA intake on LDL–C, particularly in the low dose region of the response curve where IP–TFA intake is between zero and 3%en (Ref. 19). According to Allen et al., an S-shaped model with an assumed threshold at low IP–TFA doses explained more of the study-to-study variability compared to the linear dose-response model (Ref. 18). Using assumptions about intra-individual measurement variation for LDL–C and the S-shaped model, the authors concluded that the change in LDL–C associated with a change in IP–TFA intake of 2.2%en represented a biologically meaningless change (Ref. 18). The petition stated that this analysis supports the existence of a threshold level of IP–TFA intake, below which negligible changes in LDL–C would occur.

FDA Assessment

We do not agree that these two studies cited by the petitioner provide convincing evidence to refute a linear dose-response or provide convincing evidence of a threshold in the effect of IP–TFA on LDL–C. In our review, we identified several design flaws and questionable data interpretations associated with these two studies (Ref. 7). One major concern about the MOA paper (Ref. 17) is that the authors relied largely on data from laboratory animal models to hypothesize an MOA that suggests the existence of a threshold effect of TFA on LDL–C in humans, despite the differences in biological response to dietary fats and fatty acid metabolism between humans and the animal species used in the study (*e.g.,* rodents). The authors acknowledged that *trans* fatty acids such as elaidic acid do not increase serum LDL–C in hamsters, and suggest that animal models may underestimate the effect of TFA in humans (Ref. 17).[5]

Regarding the meta-regression paper (Ref. 18), we found that duplicate data points were erroneously used in the analysis; the validity of data points for low TFA levels below 3%en was questionable, and the low TFA data did not come from PHO test diets; and incorrect variances were applied in the weighting of the data based on the study designs (Ref. 7). We also question the authors' suggestion that the within person, day-to-day variability of blood LDL–C levels can be used to represent the minimum increment in LDL–C that is adverse (Ref. 7). Additionally, we note that the authors' proposed S-shaped dose-response model that levels off at high *trans* fat doses (above 3%en) is not consistent with the results of numerous controlled feeding trials of IP–TFA at higher doses or with prospective observational studies which show increases in serum LDL–C levels or CHD risk with higher intakes of *trans* fat (Ref. 7).

E. Risk Estimates and Safety Arguments

The petition contained an estimate of ''hypothetical change'' in CHD risk associated with 0.05%en IP–TFA intake (the daily amount of energy from IP–TFA contributed by the petitioned uses of PHOs) that was based on FDA's four deterministic quantitative risk assessment methods referenced in the declaratory order (Ref. 4). The petitioner stated that they included this analytical approach in the petition ''for expediency and at the request of FDA'', although the petition questioned the validity of a linear-no threshold dose-response model for IP–TFA intake and LDL–C and HDL–C on which the FDA method is based. The deterministic quantitative risk assessment approach used by the petitioner estimated the change in CHD risk due to effects on blood lipoproteins from controlled feeding trials, and also estimated the change in CHD risk using direct observations of CHD from prospective studies when there is an isocaloric replacement of *cis*-MUFA with IP–TFA in the diet. The petitioner estimated that the change in CHD risk associated with a 0.05%en added IP–TFA intake from petitioned uses ranged from 0.062 percent to 0.665 percent depending on the risk method used. When expressed as a population-based risk estimate, the annual probability of CHD cases per 100,000 U.S. adults aged 35 and older ranged from 0.42 to 4.54. In other words, for every 100,000 U.S. adults, there could be up to 4.54 additional cases (fatal and non-fatal) of CHD attributed to an intake of 0.05%en IP–TFA from the petitioned uses of PHOs.

The petition asserts a standard of ''*de minimis* risk.'' According to the petitioner, a de minimis risk implies that a risk is so small that it should be ignored, and the petitioned use should be considered safe. The petitioner referenced three arguments to explain its de minimis risk principle: (1) The probability of a risk is below an acceptable cutoff (*i.e.,* ''bright line'' or threshold); (2) there is a lack of scientific data to establish that the risk exists (*i.e.,* the risk is non-detectable); or (3) the probability of the risk is less than the natural occurrence of the risk (Ref. 20). While neither the FD&C Act nor FDA's regulations regarding the evaluation of the safety of food additives in response to a food additive petition refer to de minimis risk, we review each of these arguments in turn.

[5] The scientific evidence that PHOs are no longer GRAS for use in food was not based on animal studies, such as those used in the Reichard and Haber MOA, but rather included results from controlled feeding studies on *trans* fatty acid consumption in humans, findings from long-term prospective epidemiological studies in human populations, and the opinions of expert panels that there is no threshold intake level for IP–TFA that would not increase an individual's risk of CHD (78 FR 67169 at 67172).

1. De minimis ''Bright Line'' or Threshold Argument

The petition referenced an article by Castorina and Woodruff (Ref. 21) in which the authors estimated risks for non-cancer health outcomes from hypothetical lifetime ingestion or inhalation exposures to select environmental chemicals at the U.S. Environmental Protection Agency's (EPA) established reference doses (RfDs) or reference concentrations. The authors concluded that the non-cancer risk associated with RfDs ranged from 1 in 10,000 (1×10^{-4}) to 5 in 1,000 (5×10^{-3}) using a linear dose-response relationship for the environmental chemicals the authors selected. The petitioner applied a safety factor to the authors' risk estimates associated with RfDs to arrive at a proposed probability of risk, ranging from 2 in 100,000 (2×10^{-5}) to 1 in 1,000 (1×10^{-3}), which the petitioner deemed to be a de minimis risk. The petitioner compared this risk range to the results of their quantitative risk estimate, which predicted the annual probability of CHD cases attributed to 0.05%en IP–TFA intake from the petitioned PHO uses to be in the range of 0.42 per 100,000 adults (or 4.2×10^{-6}) to 4.5 per 100,000 adults (or 4.5×10^{-5}). The petition concluded that the estimated risk from 0.05%en IP–TFA intake from petitioned PHO uses is de minimis because it is well below the probable de minimis risk ranges for non-cancer risk calculated by applying a safety factor to the risks presented in the Castorina and Woodruff article.

FDA Assessment

We will first address the petitioner's reliance on the Castorina and Woodruff paper to determine the concept of de minimis risk, followed by our comments on the petitioner's deterministic risk assessment. We will also include a discussion of the probabilistic risk assessment that we conducted as part of our review.

a. Castorina and Woodruff Study

We disagree with the petitioner's interpretation of the Castorina and Woodruff article on which the petitioner's safety conclusion is based. The application of the Castorina and Woodruff study results has limitations as a basis for inferring that IP–TFA from petitioned PHO uses is safe because it represents de minimis risk. The study is a single, exploratory analysis of whether EPA reference values represent negligible risk levels; it is not a consensus that defines a concept of de minimis risk or safe exposure. In fact, the study authors themselves question whether the non-cancer risks associated with the EPA's reference values represent ''acceptable levels'' of exposure from a public health perspective (Ref. 21). Furthermore, we note that in the Castorina and Woodruff paper, the estimated risks were based on biochemical and physiological changes associated with several non-cancer health outcomes that are much less serious than CHD cases or CHD deaths. For example, some of the biochemical and physiological changes the authors considered included small intestinal lesions, fatty cyst formation in the liver, elevated serum glutamate-pyruvate transaminases, chronic irritation of stomach, decreased lymphocyte count, changes in red blood cell volumes, decreased mean terminal body weights, and decreased maternal body weight gain. Therefore, we conclude that the petitioner's use of this single article to support their de minimis risk argument regarding the risk of CHD or CHD death associated with IP–TFA exposure is inadequate.

b. Petitioner's Quantitative Deterministic Risk Assessment

The petitioner relied on the de minimis risk principle to conclude that the petitioned uses of PHOs are safe because the estimated probability of CHD risk associated with IP–TFA from the petitioned uses of PHOs falls below the probable de minimis non-cancer risk range. The petition included a quantitative deterministic risk assessment that estimated the annual probability of CHD cases that may be associated with IP–TFA from petitioned uses of PHOs ranged from 0.42 to 4.54 per 100,000 U.S. adults. We note, though, that the petition did not include an estimated annual number of CHD cases or estimated annual number of CHD deaths associated with IP–TFA from the proposed uses of PHOs. Using the petitioner's estimated annual rate of CHD cases per 100,000 adults, the U.S. Census estimate of 166.7 million adults in the U.S. population in 2014, and a 32 percent CHD fatality rate reported by the Centers for Disease Control and Prevention (CDC), we expanded the petitioner's risk estimates associated with IP–TFA from petitioned uses of PHOs to estimate a range of 700 to 7,570 cases of CHD per year including between 224 and 2,422 deaths from CHD per year, which FDA does not consider to be insignificant (Ref. 7). Additionally, we conducted our own deterministic risk assessment to verify that the petitioner's methods were appropriate, and we expanded our analysis to include a probabilistic risk assessment to further bolster our decision that the estimated risks associated with the petitioned uses of PHOs cause them to be unsafe food additives (Ref. 6).

c. FDA's Quantitative Probabilistic Risk Assessment

The deterministic risk assessment approach that was used by both the FDA in our declaratory order and by the petitioner in FAP 5A4811 to assess CHD risk associated with IP–TFA exposure is a risk assessment approach using assigned values for discrete scenarios (*e.g.,* using most likely scenarios or mean values) (Ref. 6). The deterministic approach determines the robustness of the risk of CHD. However, it has limitations in that it is inadequate in applying population or other parameter variability information and it takes into consideration only a few discrete results (*e.g.,* mean risk estimates), overlooking many others (*e.g.,* probability distributions of risk estimates). The impact of different risk parameter values and uncertainty in risk methods relative to results also cannot be quantified (Ref. 6).

The probabilistic approach allows for the analysis of human variability and uncertainty in the risk method to be incorporated into both the exposure and risk assessments, if high quality empirical data with the probability distribution information for key parameters are used in the risk assessment (Ref. 6). We considered that at the petitioned IP–TFA exposure of 0.05%en, there would be greater uncertainty in the CHD risk estimates than the IP–TFA exposure of 0.5%en which was used in the declaratory order, and that the mean risk estimates alone would not be sufficient to demonstrate safety. Therefore, we conducted a probabilistic risk assessment for the CHD risk associated with an IP–TFA exposure of 0.05%en taking into consideration the variability and uncertainty associated with IP–TFA exposure and the risk parameters, and estimated both the probabilistic means and the uncertainty around the means.

We used FDA's four risk methods based on a linear no-threshold dose-response model (Ref. 6) to estimate changes in CHD risk when replacing *cis*-MUFA or saturated fatty acids at 0.05%en, with the same percentage of energy from IP–TFA. The probabilistic means were in line with the results estimated using the deterministic approach. The probabilistic approach also quantified the probability distribution of the risk estimates (*e.g.,* the lower and upper 95 percent statistical uncertainty intervals (95

percent UIs)). The results included estimated changes in percent CHD risk, increases in the rate of annual CHD cases (both fatal and non-fatal) per 100,000 U.S. adults, and increases in the number of annual CHD cases, including CHD deaths, among U.S. adults. We also extended Method 4 (prospective observational studies) to estimate the annual number of CVD deaths among this same population. (CVD deaths include deaths from CHD, strokes, and other vascular diseases.) Our assessment methodology is documented in our review memorandum (Ref. 6).

Results from our probabilistic risk assessment demonstrate that consuming IP–TFA at a level of 0.05%en per person per day, instead of *cis*-MUFA, can cause a mean increase in annual CHD cases per 100,000 U.S. adults from 0.478 (95 percent UI 0.299 to 0.676) using the FDA risk method based on changes of LDL–C alone (Method 1) to 4.038 (95 percent UI 2.120 to 6.280) using the FDA risk method based on prospective observational studies (Method 4). These increases correspond to a mean increase in annual CHD cases from 814 (95 percent UI 510 to 1,151, using Method 1) to 6,877 (95 percent UI 3,611 to 10,694, using Method 4), which includes annual deaths from CHD from 290 (95 percent UI 182 to 410, using Method 1) to 2,450 (95 percent UI 1,287 to 3,811, using Method 4). The other two FDA risk methods produced increases in risk values from CHD that were between those estimated by Method 1 and Method 4.

The same amount of IP–TFA replacing saturated fatty acids would result in lower estimates of annual CHD cases and CHD-related deaths than those estimated by replacing *cis*-MUFA with IP–TFA. We estimated the mean increase in annual CHD cases to be 170 (using Method 1) to 5,110 (using Method 4), which includes 60 to 1,821 annual deaths from CHD. Using extended Method 4, the same amount of IP–TFA replacing either saturated fatty acids or carbohydrate could cause more than 6,500 CVD deaths per year in U.S. adults. The results of our analyses are described further in our review memorandum (Ref. 6).

Our deterministic and probabilistic quantitative risk assessments demonstrate that there is a probable significant health risk associated with 0.05%en from IP–TFA from the petitioned uses of PHOs. Our analyses do not support the petitioner's claims that 0.05%en from IP–TFA results in de minimis risk or that there is a reasonable certainty that PHOs are not harmful under the intended conditions of use.

2. Non-Detectability Argument

The petitioner argued that the estimated exposure to IP–TFA from petitioned uses of PHOs (*i.e.,* 0.05%en) is well below the exposure levels in controlled feeding studies and effects at these low IP–TFA levels cannot be empirically established based on the currently available evidence. The petition questioned the appropriateness of using a linear dose-response model for quantifying the effect of lower levels of *trans* fat intake (*i.e.,* <3%en) on LDL–C and HDL–C, and maintained that there is a general lack of empirical evidence that consumption of low levels of *trans* fat increases CHD risk due to an adverse effect on blood lipoproteins. The petition highlighted one study (Ref. 18) suggesting that a linear dose-response model was not appropriate for quantifying effects of lower levels of IP–TFA intake on LDL–C. In addition, the petition noted that the *trans* fat content of control diets used in published feeding studies ranged from non-detectable to 2.4%en and suggested, by example, that the non-detectable level of TFA in a test diet could be at 0.15%en, which is three times higher than IP–TFA from petitioned uses of PHOs. Moreover, the petition noted that overall the IP–TFA intake from petitioned uses of PHOs (0.05%en) is well below the intake level of diets tested in the controlled feeding trials that were relied upon in the meta-analyses to assess the effect of IP–TFA on CHD risk. Because the impact of low level IP–TFA intakes cannot be detected by scientific studies, the petition concluded that the IP–TFA intake from petitioned uses of PHOs could be considered de minimis.

FDA Assessment

We will address the petitioner's non-detectability argument with a three-prong response. First, we will discuss the issue of statistical power and how it relates to detectable changes in clinical feeding trials. Next, we will review empirical evidence of adverse effects of lower IP–TFA intakes from several recent population studies. Lastly, we will comment on the body of evidence that supports a no-threshold, linear dose-response model to characterize the adverse health effects of *trans* fat intake.

a. Statistical Power of Controlled Feeding Trials

Statistical power is the probability that a study will correctly detect an effect when an effect exists (Ref. 22). Larger sample sizes generally result in higher statistical power, increasing the likelihood that a study will be able to identify differences in the study subjects. We acknowledge that there are limits to the statistical power of controlled feeding trials to measure changes in LDL–C from low levels of TFA exposure. However, the lack of data from controlled feeding trials on the effect of TFA intake on blood lipids at lower TFA intake is not due to a potential threshold below which TFA intake has no effect on LDL–C and other blood lipids. Rather, the lack of data at lower TFA intake is due to the limited statistical power to detect significant changes in LDL–C at TFA intake below about 3 percent of energy in controlled feeding trials with feasible sample size of about 100 participants. For example, we estimated that it would require more than 300,000 participants in hypothetical PHO feeding trials to detect statistically significant changes LDL–C at the IP–TFA dietary exposure of 0.05%en (Refs. 6 and 7).

b. Empirical Evidence From New Population Studies

Recent population studies have shown empirical evidence of adverse effects of lower IP–TFA intake levels on CHD risk. Two recent prospective observational studies with long term follow-up found significant increases in CHD risk or CVD mortality at *trans* fat intake increments as low as 0.3%en to 0.6%en (Refs. 15 and 16). This is about 1/10 of the approximately 3 percent of energy from TFA intake that can be studied in controlled feeding trials of lipid biomarkers, and is roughly tenfold higher than the 0.05%en IP–TFA exposure from petitioned PHO uses.

Two recent studies independently examined the public health effects of restricting *trans* fat in eateries in several New York state counties between 2007 and 2011 (Refs. 23 and 24). In one study, the authors compared records of hospital admissions for heart attack and stroke in counties that had TFA restrictions and in control counties that had no restrictions (Ref. 23). They found that there was an additional 6.2 percent decline in hospital admissions for heart attacks and strokes in the populations of counties with TFA restrictions. This reduction corresponds to 43 CVD events prevented annually per 100,000 persons. In another study, the authors analyzed the association of *trans* fat restrictions in certain New York state counties and annual CVD mortality rates (Ref. 24). They found a 4.5 percent decrease in CVD mortality in counties with *trans* fat restrictions compared with control counties. This reduction corresponds to 13 fewer CVD deaths annually per 100,000 persons. Both studies, using separate data sources, showed consistent results of a ''real-

world'' public health impact associated with the removal of *trans* fat in restaurant food.

Four studies published in 2017 examined data on plasma *trans* fatty acid concentrations in U.S. adults from the NHANES of 1999–2000 and 2009–2010 (Refs. 25–28). These studies showed the association between plasma TFA and serum lipid and lipoprotein (*i.e.,* LDL–C and HDL–C) concentration before and after reductions in TFA consumption occurred in the U.S. population. On average, plasma TFA concentrations in U.S. adults were about 54 percent lower in 2009–2010 compared to 1999–2000 (Refs. 26 and 27). Significant improvements in blood lipids (*e.g.,* lower LDL–C and triglycerides, higher HDL–C) occurred over time as plasma TFA concentrations decreased (Refs. 25 and 26). Despite substantial reductions in TFA intake over time, plasma TFA concentrations were significantly and consistently associated with serum lipid and lipoprotein concentrations at both time periods (Ref. 27). Results were similar for metabolic syndrome and most of its components such as large waistline, high fasting glucose, and high triglycerides (Ref. 28). The authors concluded that these studies do not support the existence of a threshold under which the association between plasma TFA concentration and lipid profiles might become undetectable (Refs. 27 and 28).

c. Consistent Support of a Progressive and Linear Dose-Response

In response to the petitioner's argument of a non-linear dose-response, we note that the vast majority of scientific studies have been consistent in their conclusions that *trans* fat consumption has a progressive and linear adverse effect on blood lipids and CHD risk (Ref. 7). FDA's 2015 review of the scientific evidence for human health effects of TFA concluded: (1) There is no evidence of a threshold below which TFA does not affect blood lipids and (2) both controlled feeding trials and prospective observational studies strongly support the conclusion that *trans* fat intake has a progressive and linear effect that increases CHD risk, with no evidence of a threshold (Ref. 2). Numerous expert panels discussed in our 2015 review and in the current review also support this conclusion. Additional evidence from newer studies also supports the conclusion that TFA has a progressive and linear adverse effect on blood lipids and CHD risk (Refs. 12 and 29). This is discussed in detail in our review memorandum (Ref. 7).

3. Natural Occurrence Argument

The petitioner based its third argument on a ''natural occurrence'' theory which purports that a risk due to human activity may be de minimis and would not cause the activity to be considered unsafe provided that the risk does not exceed the natural occurrence of the same risk (Ref. 20). Specifically, the petitioner argued that the petitioned uses of PHOs are safe because the incremental increase in IP–TFA intake from petitioned PHO uses (*i.e.,* 0.05%en) is infinitesimally small and negligible in comparison to existing background dietary TFA exposure from intrinsic sources. As described in section IV.B, the petitioner estimated the mean exposure to TFA from intrinsic sources (*e.g.,* naturally-occurring TFA from meat and dairy foods) to be 0.46%en. The petition stated that the estimated intake of IP–TFA of 0.05%en from petitioned uses of PHOs equates to the 1.2th percentile of the TFA intake distribution from intrinsic sources. The petition explained further that this amount of IP–TFA intake is within the variability of the TFA intake from intrinsic sources and below the 5th percentile. Thus, the petition concluded that the petitioned uses are safe because the incremental increase in IP–TFA exposure from the petitioned uses of PHOs is infinitesimally small and negligible in comparison to existing background dietary TFA exposure from intrinsic sources.

FDA Assessment

For our safety assessment, we considered as a worst-case scenario the assumption that TFA from intrinsic sources is chemically and pharmacologically related to IP–TFA from PHOs. In general, TFA from intrinsic sources and IP–TFA contain the same *trans* fatty acid isomers, although in different proportions (Ref. 12). The most recent evidence from controlled feeding trials shows comparable effects on blood lipoproteins such as LDL–C and HDL–C by naturally-occurring TFA and IP–TFA (Ref. 7). Results of prospective observational studies specifically of TFA from intrinsic sources (rather than total TFA) are relatively sparse, and generally do not show an association of naturally-occurring TFA with CHD risk, possibly due to limitations of the studies (Ref. 7). Regarding the effect of TFA from intrinsic sources on adverse health outcomes other than CHD (*e.g.,* metabolic syndrome and diabetes), study results are divergent (Refs. 6 and 7). Although there are inconsistencies in the data overall, we considered for the purposes of our safety assessment that TFA from intrinsic sources is, in general, chemically and pharmacologically related to IP–TFA from PHOs.

We disagree with the petitioner's assertion that the IP–TFA exposure from the petitioned uses of PHOs is safe because it is insignificant in comparison to existing background dietary TFA exposure. We note that the per capita IP–TFA intake of 0.05%en from petitioned uses of PHOs is approximately 10 percent of mean TFA intake from intrinsic sources; we do not consider this to be an infinitesimally small or negligible amount. The contribution of IP–TFA intake from petitioned uses of PHOs is not trivial, but rather will increase the mean population TFA exposure by 10 percent. Food sources of naturally-occurring TFA are widely consumed in the population, and therefore few members of the population consume 0.05%en TFA or less. As the petition indicated, 0.05%en from IP–TFA from petitioned uses of PHOs corresponds to about the 1.2th percentile of population TFA intake from intrinsic sources. We assert that this comparison is not particularly relevant to whether the per capita IP–TFA intake is significant because the contribution of IP–TFA exposure from the petitioned uses is in addition to, not substitutional for, exposure to TFA from intrinsic sources. Rather, the relevant comparison is that the per capita IP–TFA intake, 0.05%en, is approximately 10 percent of mean TFA intake from naturally-occurring sources. For these reasons, we disagree with the petitioner's argument that the petitioned uses of PHOs are safe because they are negligible in comparison to existing background dietary TFA exposure from intrinsic sources.

As stated earlier, there is no explicit reference to de minimis risks under either the FD&C Act or FDA's regulations regarding the evaluation of the safety of food additives in response to a food additive petition. Based on the data submitted by the petitioner, FDA has determined that the petitioned uses present more than a de minimis or negligible risk. Therefore, FDA has not found it necessary as part of its petition response to determine how the concept of de minimis risk may apply to the safety analysis under section 409 of the FD&C Act.

V. Comments on the Filing Notification

We received 10 comments in response to the petition's filing notification. Seven comments expressed opposition to the petition, one comment was about

labeling of PHOs, one comment did not pertain to the petition, and one comment was a duplicate submission. All of the comments opposing the petition cited the adverse health effects associated with the consumption of TFA. None of the comments provided information to support the petitioner's conclusion that the proposed uses of PHOs are safe.

VI. Conclusion

FAP 5A4811 requested that the food additive regulations be amended to provide for the safe use of PHOs as a solvent or carrier for flavoring agents, flavor enhancers, and coloring agents; as a processing aid; and as a pan release agent for baked goods at specific use levels. After reviewing the petition, as well as additional data and information relevant to the petitioner's request, we determined that the petition does not contain convincing evidence to support the conclusion that the proposed uses of PHOs are safe. Therefore, FDA is denying FAP 5A4811 in accordance with 21 CFR 171.100(a).

VII. Compliance Date

As discussed in section II, the declaratory order concluded that PHOs are no longer GRAS for any use in human food and established a compliance date of June 18, 2018 (80 FR 34650). In light of our denial of FAP 5A4811, we acknowledge that the food industry needs additional time to identify suitable replacement substances for the petitioned uses of PHOs and that the food industry has indicated that 12 months could be a reasonable timeframe for reformulation activities (Ref. 30). Therefore, elsewhere in this issue of the **Federal Register**, we have extended the compliance date to June 18, 2019, for the manufacturing of food with the petitioned uses of PHOs. Food manufactured with the petitioned uses after June 18, 2019 may be subject to enforcement action by FDA.

In addition, for food manufactured with the petitioned uses before June 18, 2019, elsewhere in this issue of the **Federal Register**, we are extending the compliance date to January 1, 2021. This time frame will allow manufacturers, distributors, and retailers to exhaust product inventory of foods made with the petitioned uses before the manufacturing compliance date. All foods containing unauthorized uses of PHOs after January 1, 2021 may be subject to FDA enforcement action.

VIII. Objections

Any persons that may be adversely affected by this document 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.

It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.* We will publish notice of the objections that we have received or lack thereof in the **Federal Register**.

IX. References

The following references are on display in the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Sacks, F.M., A.H. Lichtenstein, J.H.Y. Wu, et al. ''Dietary Fats and Cardiovascular Disease: A Presidential Advisory from the American Heart Association.'' *Circulation* 136(3): e1–e23, 2017.
2. FDA Memorandum from J. Park to M. Honigfort, Scientific Update on Experimental and Observational Studies of *Trans* Fat Intake and Coronary Heart Disease Risk, June 11, 2015.
3. FDA Memorandum from J. Park to M. Honigfort, Literature Review, June 11, 2015.
4. FDA Memorandum from J. Park to M. Honigfort, Quantitative Estimate of Industrial *Trans* Fat Intake and Coronary Heart Disease Risk, June 11, 2015.
5. FDA Memorandum from D. Doell to E. Anderson, April 13, 2018.
6. FDA Memorandum from J. Park to E. Anderson, Quantitative Coronary Heart and Cardiovascular Disease Risk Assessments of Exposure from Industrially-Produced *Trans* Fatty Acid (IP–TFA) from Proposed Uses of Partially Hydrogenated Vegetable Oils (PHO) in Select Foods, April 16, 2018.
7. FDA Memorandum from J. Park to E. Anderson, Scientific Literature Review Update on *Trans* Fats with Detailed Responses to the Petitioner's Safety Conclusions on the Petitioned Uses of Partially Hydrogenated Oils (PHOs), April 16, 2018.
8. IOM/NAS, ''Dietary Reference Intakes for Energy Carbohydrate, Fat, Fatty Acids, Cholesterol, and Amino Acids (Macronutrients),'' National Academies Press, Washington, DC, 2002/2005, Available at: *https://www.nap.edu.*
9. Katan, M.B., P.L. Zock, and R.P. Mensink, ''*Trans* Fatty Acids and Their Effects on Lipoproteins in Humans,'' *Annual Review of Nutrition,* 15:473–93, 1995.
10. Zock, P.L., M.B. Katan, and R.P. Mensink, ''Dietary *Trans* Fatty Acids and Lipoprotein Cholesterol,'' *American Journal of Clinical Nutrition,* 61(3):617, 1995.
11. Zock, P.L. and R.P. Mensink, ''Dietary *Trans*-Fatty Acids and Serum Lipoproteins in Humans,'' *Current Opinion in Lipidology,* 7(1):34–7, 1996.
12. Brouwer, I.A., ''Effect of *Trans*-Fatty Acid Intake on Blood Lipids and Lipoproteins: A Systematic Review and Meta-Regression Analysis,'' Geneva: World Health Organization, 2016.
13. Hafekost, K., T.A. O'Sullivan, D. Lawrence, and F. Mitrou, ''Systematic Review of the Evidence for a Relationship Between *Trans*-Fatty Acids and Blood Cholesterol,'' Canberra, Australia: On behalf of Food Standards Australia New Zealand, 2014, available at: *http://www.foodstandards.gov.au/publications/Pages/Systematic-Review-of-the-evidence-for-a-relationship-between-trans-fatty-acids-and-blood-cholesterol-.aspx.*
14. de Souza, R.J., A. Mente, A. Maroleanu, et al., ''Intake of Saturated and *Trans* Unsaturated Fatty Acids and Risk of All Cause Mortality, Cardiovascular Disease, and Type 2 Diabetes: Systematic Review and Meta-Analysis of Observational Studies,'' BMJ, 351:h3978, 2015.
15. Li, Y., Hruby, A., A.M. Bernstein, et al., ''Saturated Fats Compared with Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study,'' *Journal of the American College of Cardiology,* 66(14):1538–48, 2015.
16. Wang, D.D., Y. Li, S.E. Chiuve, et al., ''Association of Specific Dietary Fats with Total and Cause-Specific Mortality,'' *JAMA Internal Medicine,* 176(8):1134–45, 2016.
17. Reichard, J.F. and L.T. Haber, ''Mode-of-Action Evaluation for the Effect of *Trans* Fatty Acids on Low-Density Lipoprotein Cholesterol,'' *Food and Chemical Toxicology,* 98(Pt B):282–94, 2016.
18. Allen, B.C., M.J. Vincent, D. Liska, and L.T. Haber, ''Meta-Regression Analysis of

the Effect of *Trans* Fatty Acids on Low-Density Lipoprotein Cholesterol,'' *Food and Chemical Toxicology,* 98(Pt B):295–307, 2016.
19. Liska, D.J., C.M. Cook, D.D. Wang, P.C. Gaine, and D.J. Baer, ''*Trans* Fatty Acids and Cholesterol Levels: An Evidence Map of the Available Science.'' *Food and Chemical Toxicology,* 98(Pt B):269–81, 2016.
20. Peterson, M., ''What is a *de minimis* Risk?'' *Risk Management: An International Journal,* 4(2):47–55, 2002.
21. Castorina, R. and T.J. Woodruff, ''Assessment of Potential Risk Levels Associated with U.S. Environmental Protection Agency Reference Values,'' *Environmental Health Perspectives,* 111(10):1318–25, 2003.
22. Rosner, B., *Fundamentals of Biostatistics,* Duxbury Press, Belmont, CA, 2010.
23. Brandt, E.J., R. Myerson, M.C. Perraillon, and T.S. Polonsky, ''Hospital Admissions for Myocardial Infarction and Stroke Before and After the *Trans*-Fatty Acid Restrictions in New York,'' *JAMA Cardiology,* 2(6):627–634, 2017.
24. Restrepo, B.J. and M. Rieger, ''*Trans* Fat and Cardiovascular Disease Mortality: Evidence from Bans in Restaurants in New York,'' *Journal of Health Economics,* 45:176–96, 2016.
25. Restrepo, B.J., ''Further Decline of *Trans* Fatty Acids Levels Among US Adults Between 1999–2000 and 2009–2010,'' *American Journal of Public Health,* 107(1):156–8, 2017.
26. Vesper, H.W., S.P. Caudill, H.C. Kuiper, et al., ''Plasma *Trans*-Fatty Acid Concentrations in Fasting Adults Declined from NHANES 1999–2000 to 2009–2010,'' *American Journal of Clinical Nutrition,* 105(5):1063–9, 2017.
27. Yang, Q., Z. Zhang, F. Loustalot, et al., ''Plasma *Trans*-Fatty Acid Concentrations Continue to be Associated with Serum Lipid and Lipoprotein Concentrations Among US adults After Reductions in *Trans*-Fatty Acid Intake,'' *Journal of Nutrition,* 147(5):896–907, 2017.
28. Zhang, Z., C. Gillespie, Q. Yang, ''Plasma *Trans*-Fatty Acid Concentrations Continue to be Associated with Metabolic Syndrome Among US Adults After Reductions in *Trans*-Fatty Acid Intake,'' *Nutrition Research,* 43:51–9, 2017.
29. Mensink, R.P., ''Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis,'' Geneva: World Health Organization, 2016.
30. Letter from the American Bakers Association, et al., to Dr. Scott Gottlieb, Commissioner, Food and Drug Administration (April 30, 2018) (sent by electronic mail).

Dated: May 15, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018–10715 Filed 5–18–18; 8:45 am]

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

33 CFR Part 100

[Docket Number USCG–2018–0296]

RIN 1625–AA08

Special Local Regulation; North Atlantic Ocean, Ocean City, MD

AGENCY: Coast Guard, DHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Coast Guard is proposing to establish special local regulations for certain waters of the North Atlantic Ocean. This action is necessary to provide for the safety of life on these navigable waters located at Ocean City, Worcester County, MD, during a high-speed power boat racing event on June 23, 2018, and June 24, 2018. This proposed rulemaking would prohibit persons and vessels from being in the regulated area unless authorized by the Captain of the Port Maryland-National Capital Region or Coast Guard Patrol Commander. We invite your comments on this proposed rulemaking.

DATES: Comments and related material must be received by the Coast Guard on or before June 20, 2018.

ADDRESSES: You may submit comments identified by docket number USCG–2018–0296 using the Federal eRulemaking Portal at *http://www.regulations.gov.* See the ''Public Participation and Request for Comments'' portion of the **SUPPLEMENTARY INFORMATION** section for further instructions on submitting comments.

FOR FURTHER INFORMATION CONTACT: If you have questions about this proposed rulemaking, call or email Mr. Ronald Houck, U.S. Coast Guard Sector Maryland-National Capital Region; telephone 410–576–2674, email *Ronald.L.Houck@uscg.mil.*

SUPPLEMENTARY INFORMATION:

I. Table of Abbreviations

CFR Code of Federal Regulations
DHS Department of Homeland Security
FR Federal Register
NPRM Notice of proposed rulemaking
Pub. L. Public Law
§ Section
U.S.C. United States Code

II. Background, Purpose, and Legal Basis

On January 30, 2018, the Offshore Powerboat Association of Brick Township, NJ, notified the Coast Guard through submission of a marine event application that this year's Ocean City Grand Prix would be held on a different date this year from that published in the Code of Federal Regulations (CFR) at Table to 33 CFR 100.501 at (b.)19. The estimated date for this annual event listed in the regulation is either the first or second Saturday or Sunday of May, or the second or third Saturday and Sunday of September. This year, the Ocean City Grand Prix is being held on June 23, 2018, and June 24, 2018. The high-speed power boat racing consist of approximately 40 participating offshore race boats of various classes, 21 to 50 feet in length, operating along a designated, marked racetrack-type course located in the North Atlantic Ocean, at Ocean City, MD. Details of the proposed event were provided to the Coast Guard on March 12, 2018. Hazards from the power boat racing event include participants operating near a designated navigation channel, as well as injury to persons and damage to property that involve vessel mishaps during high-speed power boat races conducted on navigable waters located near the shoreline. The Captain of the Port (COTP) Maryland-National Capital Region has determined that potential hazards associated with the power boat races would be a safety concern for anyone intending to operate within certain waters of the North Atlantic Ocean at Ocean City, MD.

The purpose of this rulemaking is to protect event participants, spectators and transiting vessels on certain waters of North Atlantic Ocean before, during, and after the scheduled event. The Coast Guard proposes this rulemaking under authority in 33 U.S.C. 1233, which authorize the Coast Guard to establish and define special local regulations.

III. Discussion of Proposed Rule

The COTP Maryland-National Capital Region is proposing to establish special local regulations that will be enforced from 9:30 a.m. to 5:30 p.m. on June 23, 2018 and from 9:30 a.m. to 5:30 p.m. on June 24, 2018. The regulated area is a polygon in shape measuring approximately 4,500 yards in length by 1,600 yards in width. The area would cover all navigable waters of the North Atlantic Ocean, within an area bounded by the following coordinates: Commencing at a point near the shoreline at latitude 38°21′42″ N, longitude 075°04′11″ W, thence east to latitude 38°21′33″ N, longitude 075°03′10″ W, thence southwest to latitude 38°19′25″ N, longitude 075°04′02″ W, thence west to the shoreline at latitude 38°19′35″ N, longitude 075°05′02″ W, at Ocean City, MD.