



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1317]

Final Determination Regarding Partially Hydrogenated Oils

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; declaratory order.

SUMMARY: Based on the available scientific evidence and the findings of expert scientific panels, the Food and Drug Administration (FDA or we) has made a final determination that there is no longer a consensus among qualified experts that partially hydrogenated oils (PHOs), which are the primary dietary source of industrially-produced trans fatty acids (IP-TFA) are generally recognized as safe (GRAS) for any use in human food. This action responds, in part, to citizen petitions we received, and we base our determination on available scientific evidence and the findings of expert scientific panels establishing the health risks associated with the consumption of trans fat.

DATES: Compliance date: Affected persons must comply no later than June 18, 2018.

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SUPPLEMENTARY INFORMATION:

Table of Contents

- I. Background
- II. Definitions and Scope, and Related Comments With FDA Responses
- III. Discussion of Legal Issues, and Related Comments With FDA Responses
 - A. GRAS
 - B. Prior Sanctions
 - C. Procedural Requirements
- IV. Discussion of Scientific Issues, and Related Comments With FDA Responses
 - A. Intake Assessment
 - B. Safety
- V. Citizen Petitions
- VI. Environmental Impact
- VII. Economic Analysis
- VIII. Compliance Date and Related Comments With FDA Responses
- IX. Conclusion and Order
- X. References

I. Background

In accordance with the process set out in § 170.38(b)(1) (21 CFR 170.38(b)(1)), we issued a notice on November 8, 2013 (the November 2013 notice, 78 FR 67169), announcing our tentative determination that, based on currently available scientific information, PHOs are no longer GRAS under any condition of use in human food and therefore are food additives subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 348).

FDA's evaluation of the GRAS status of PHOs centers on the trans fatty acid (TFA, also referred to as "trans fat") component of these oils. Although we primarily use the word "oil"

when discussing PHOs in this document, partially hydrogenated fats (such as partially hydrogenated lard), are included within the definition of PHOs (discussed in section II) and therefore within the scope of this order, and references to “oil” in this document should be read in most cases to include fats. PHOs are the primary dietary source of industrially-produced trans fatty acids (Ref. 1). As explained in the tentative determination (78 FR 67169), all refined edible oils contain some trans fat as an unintentional byproduct of their manufacturing process; however, unlike other edible oils, trans fats are an integral component of PHOs and are purposely produced in these oils to affect the properties of the oils and the characteristics of the food to which they are added. In addition, the trans fat content of PHOs is significantly greater than the amount in other edible oils. Non-hydrogenated refined oils may contain trans fatty acids as a result of high-temperature processing, at levels typically below 2 percent (Ref. 2). Low levels (below 2 percent) may also be found in fully hydrogenated oils (FHOs) due to incomplete hydrogenation (Ref. 3). Small amounts (typically around 3 percent) may be found in the fat component of dairy and meat products from ruminant animals (Ref. 4).

FDA’s tentative determination identified the significant human health risks associated with the consumption of trans fat (78 FR 67169 at 67171). The tentative determination was based on evidence including results from a number of controlled feeding studies on trans fatty acid consumption in humans (Refs. 5 and 6), findings from long-term prospective epidemiological studies (Refs. 5 and 6), and the opinions of expert panels (Refs. 7, 8, 9, 10, 11, 12, 13, and 14). The latter included the 2005 recommendation of the Institute of Medicine (IOM) to limit trans fat consumption as much as possible while consuming a nutritionally adequate diet, recognizing that trans fat occurs naturally in meat and dairy products from ruminant animals and that naturally-occurring trans fat is unavoidable in ordinary, non-vegan

diets without significant dietary adjustments that may introduce undesirable effects (Ref. 7). In addition, in the tentative determination FDA cited a peer reviewed, published estimate of deaths and coronary events that would be prevented annually in the United States from elimination of remaining uses of PHOs from the food supply (Ref. 15). Given all this evidence, we tentatively determined that there is no longer a consensus among qualified experts that PHOs, the primary dietary source of IP-TFA, are safe for human consumption, either directly or as ingredients in other food products.

PHOs have a long history of use as food ingredients. The two most common PHOs currently used by the food industry, partially hydrogenated soybean oil and partially hydrogenated cottonseed oil, are not listed as GRAS or as approved food additives in FDA's regulations. However, these and other commonly used PHOs (e.g., partially hydrogenated coconut oil and partially hydrogenated palm oil) have been considered GRAS by the food industry based on a history of use prior to 1958. By contrast, the partially hydrogenated versions of low erucic acid rapeseed oil (LEAR oil; § 184.1555(c)(2) (21 CFR 184.1555(c)(2))) and menhaden oil (§ 184.1472(b) (21 CFR 184.1472(b))) have been affirmed by regulation as GRAS for use in food. Partially hydrogenated LEAR oil was affirmed as GRAS for use in food (50 FR 3745 (January 28, 1985)) through scientific procedures. Partially hydrogenated menhaden oil was affirmed as GRAS for use in food (54 FR 38219 (September 15, 1989)) on the basis that the oil is chemically and biologically comparable to commonly used partially hydrogenated vegetable oils such as corn and soybean oils. FDA believes that partially hydrogenated LEAR and menhaden oils are not currently widely used by the food industry. We plan to amend these regulations in a future rulemaking.

In the November 2013 notice, FDA requested additional data and scientific information related to our tentative determination and, in particular, requested comment on several questions (78 FR 67169 at 67174). Interested persons were originally given until January 7, 2014, to comment on the notice. However, in response to several requests, we extended the comment period to March 8, 2014 (78 FR 79701 (December 31, 2013)).

We received over 6000 comments in response to the November 2013 notice announcing our tentative determination, including over 4500 form letters. In addition to submissions from individuals, we received comments from industry and trade associations, consumer and advocacy groups, health professional groups, and state/local governments. Most comments generally supported the tentative determination or supported aspects of it. FDA also received numerous comments stating that although they agreed with FDA's efforts to further reduce trans fat in the food supply, they disagreed with our tentative determination regarding the GRAS status of PHOs. Of the comments that objected to the tentative determination, many disagreed with FDA's scientific analysis and offered alternative approaches to address trans fat in the food supply. Some comments addressed issues outside the scope of the tentative determination (such as disruptions to trade, taxation of foods, and requests for bans on other substances) and were not considered. We reviewed all comments that were submitted to the docket before arriving at the decision outlined in this order.

We have arranged comments and our responses by topic throughout the remainder of this document. To make it easier to identify the comments and our responses, the word "Comment," in parentheses, appears before the comment's description and the word "Response," in parentheses, appears before FDA's response. Each comment is numbered to help distinguish

between different comments. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance.

The major provisions of this order are:

- PHOs are not GRAS for any use in human food.
- 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).
- For the purposes of this declaratory order, FDA is defining PHOs as those fats and oils that have been hydrogenated, but not to complete or near complete saturation, and with an iodine value (IV) greater than 4.
- FDA is establishing a compliance date of June 18, 2018.

II. Definitions and Scope, and Related Comments With FDA Responses

(Comment 1) Some comments requested that we define PHOs and clearly delineate them from FHOs. The comments suggested various parameters for defining these fats and oils, including setting a specification for trans fat content (e.g., a percentage) or using iodine value (IV; also interchangeably called iodine number).

(Response) FDA agrees with the comments that we should define PHOs to differentiate them from FHOs, which are outside the scope of this order. When a fat or oil is hydrogenated, the degree of hydrogenation can be tailored to obtain the desired properties for the application. FHOs are produced by allowing the hydrogenation process to proceed to complete or near complete saturation to obtain a more solid fat. In practice, the reaction does not proceed to 100 percent completion, even when producing FHOs, and some degree of unsaturation unavoidably remains in the final fat or oil. Non-hydrogenated refined fats and oils generally contain trans fatty acids as an unavoidable impurity as a result of high-temperature processing, at levels

typically below 2 percent (Ref. 2). The IV of a fat or oil is not a direct measure of the TFA content, but is a measure of the degree of unsaturation. Thus, in a fat or oil that has been hydrogenated, a low degree of unsaturation (i.e., a low IV number) will correlate to a low level of TFA. FHOs with an IV of 4 or less generally contain trans fat at levels similar to non-hydrogenated refined fats and oils (less than 2 percent). By contrast, when the hydrogenation process is arrested before near complete saturation, trans fat content is typically higher, and IV is typically greater than 4.

Based on data for FHOs that are currently available on the market, which are indicative of modern hydrogenation technology (Ref. 16), we define FHOs for the purposes of this order as fats and oils that have been hydrogenated to complete or near complete saturation, and with an IV of 4 or less, as determined by a method that is suitable for this analysis (e.g., ISO 3961 or equivalent). FHOs are outside the scope of this order. For the purposes of this order, we define PHOs as fats and oils that have been hydrogenated, but not to complete or near complete saturation, and with an IV greater than 4 as determined by a method that is suitable for this analysis (e.g., ISO 3961 or equivalent). These definitions will ensure that IP-TFA content in the food supply will be kept to the minimum amount feasible with current technology, except as otherwise authorized.

(Comment 2) We received several comments requesting clarification on the scope of FDA's tentative determination, including whether it applies only to PHOs used in human food; whether it applies to ingredients that contain only naturally occurring trans fat, such as those ingredients derived from ruminant sources; and whether it applies to conjugated linoleic acid. We also received a citizen petition (discussed in section V) raising questions related to partially hydrogenated methyl ester of rosin.

(Response) FDA wishes to clarify that this order applies only to PHOs used in human food, not animal feed, and applies to PHOs used as a food ingredient, which includes those uses sometimes considered processing aids or food contact substances (e.g., pan-release agents). By contrast, the use of PHOs as raw materials used to synthesize other ingredients is outside the scope of this order. We do not have specific information on the intake of industrially-produced trans fat from this source. There is no requirement that materials used to make food ingredients be GRAS themselves; rather, the resultant food ingredient must be safe for the intended conditions of use. The use of PHOs as raw materials to make other food ingredients may result in the incorporation of industrially-produced trans fats into those ingredients. When ingredients are synthesized using PHOs, and the ingredient is being used on the basis of a GRAS self-determination, reevaluation of such a determination may be appropriate in light of the health effects from the intake of trans fat that underlie our determination that PHOs do not meet the GRAS standard.

This order does not apply to ingredients that contain only naturally occurring trans fat, such as those ingredients derived from ruminant sources.

This order does not apply to the use of conjugated linoleic acid (CLA) as a food ingredient. CLA does not fit the definition of PHO. CLAs are a class of fatty acid isomers derived from linoleic acid and do not contain nonconjugated double bonds in a trans configuration nor are CLAs triglyceride molecules. On the other hand, PHOs are primarily mixtures of triglycerides, produced by partial hydrogenation and include at least one nonconjugated double bond(s) in a trans configuration (Ref. 16). Considering CLA to be distinct from PHOs is consistent with how FDA has previously defined trans fatty acids for nutrition

labeling purposes, focusing on the presence of nonconjugated bond(s) in a trans configuration (see § 101.9(c)(2)(ii) (21 CFR 101.9(c)(2)(ii))).

This order also does not apply to the use of partially hydrogenated methyl ester of rosin. Partially hydrogenated methyl ester of rosin does not fit the definition of PHO. Partially hydrogenated methyl ester of rosin is composed of resin acids that are chemically and structurally distinct from fatty acids found in PHOs. Resin acids are terpene-derived aromatic compounds that do not have long chain fatty acid components with cis/trans double bonds (Ref. 16).

III. Discussion of Legal Issues, and Related Comments With FDA Responses

A. GRAS

Section 409 of the FD&C Act provides that a food additive is unsafe unless it is used in accordance with conditions set forth in that section. “Food additive” is defined by section 201(s) of the FD&C Act (21 U.S.C. 321(s)) as any substance the intended use of which results or may reasonably be expected to result in its becoming a component or otherwise affecting the characteristics of any food, if such substance is not GRAS or otherwise excluded from the definition. Certain other substances that may become components of food are also excluded from the statutory definition of food additive, including pesticide chemicals and their residues, new animal drugs, color additives, and dietary ingredients in dietary supplements (section 201(s)(1) through (6) of the FD&C Act).

A substance is GRAS if it is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the

conditions of its intended use (section 201(s) of the FD&C Act). However, history of use prior to 1958 is not sufficient to support continued GRAS status if new evidence demonstrates that there is no longer a consensus that an ingredient is safe. See § 170.30(l) (21 CFR 170.30(l)) (“New information may at any time require reconsideration of the GRAS status of a food ingredient.”).

FDA has defined safe as “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)), and general recognition of safety must be based only on the views of qualified experts (21 CFR 170.30(a)). To establish general recognition of safety, there must be a consensus of expert opinion regarding the safety of the use of the substance. See, e.g., United States v. Western Serum Co., Inc., 666 F.2d 335, 338 (9th Cir. 1982) (citing Weinberger v. Hynson, Westcott & Dunning, 412 U.S. 609, 629-32 (1973)). General recognition of safety does not require unanimous agreement. See, e.g., United States v. Articles of Drug * * * 5,906 boxes, 745 F.2d 105, 119 n. 22 (1st Cir. 1984); United States v. Articles of Food and Drug (Coli-Trol 80), 518 F.2d 743, 746 (5th Cir. 1975) (“What is required is not unanimous recognition but general recognition.”); United States v. Articles of Drug * * * Promise Toothpaste, 624 F. Supp. 776, at 782-3 (N.D. Ill. 1985) (“There is nothing in the statute to indicate that Congress intended ‘generally recognized’ in other than its commonly understood meaning. The adverb, ‘generally,’ is defined, inter alia, to mean...extensively, though not universally” (internal quotations omitted)). Conversely, general recognition of safety does not exist if there is a lack of consensus among qualified experts that the use of a substance is safe. See, e.g., Coli-Trol 80, 518 F.2d at 746 (no general recognition of safety where there was “no recognition of the safety... of these products at all”); Premo Pharmaceutical Laboratories v. United States, 629 F.2d 795, 803-4 (2nd

Cir. 1980) (“genuine dispute among qualified experts” precludes finding of general recognition, and no general recognition existed as a matter of law where there was a “sharp difference” of expert opinion); United States v. Article of Food * * * Coco Rico, 752 F.2d 11, 15 n 6 (1st Cir. 1985) (substance was not GRAS as a matter of law based on existence of “genuine dispute among qualified experts” regarding safety of use); Promise Toothpaste, 624 F. Supp. at 783 (court could not conclude whether a “genuine dispute” existed without considering the substance of the experts’ opinions, such that a triable issue of fact existed regarding general recognition). See also United States v. Articles of Drug * * * 5,906 Boxes, 745 F.2d 105, 119 n. 22 (1st Cir. 1984) (noting certain cases in which lack of general recognition was established as a matter of law and others in which there was a triable issue of fact regarding general recognition).

Importantly, the GRAS status of a specific use of a particular substance in food may change as knowledge changes. For example, as new scientific data and information develop about a substance or the understanding of the consequences of consumption of a substance evolves, expert opinion regarding the safety of a substance for a particular use may change such that there is no longer a consensus that the specific use is safe. The fact that the status of the use of a substance under section 201(s) of the FD&C Act may evolve over time is the underlying basis for FDA’s regulation at § 170.38, which provides, in part, that we may, on our own initiative, propose to determine that a substance is not GRAS. (See generally 37 FR 6207 (March, 25, 1972) (proposal of 21 CFR 121.41, the predecessor of § 170.38); 37 FR 25705 (December 2, 1972) (issuance of 21 CFR 121.41); 35 FR 18623 (December 8, 1970) (proposal of 21 CFR 121.3, the predecessor of § 170.30); and 36 FR 12093 (June 25, 1971) (issuance of 21 CFR 121.3)). Further, as stated in section I, history of the safe use of a substance in food prior to

1958 is not sufficient to support continued GRAS status if new evidence demonstrates that there is no longer expert consensus that an ingredient is safe (§ 170.30(l)).

As noted in section III.A, under section 201(s) of the FD&C Act, a substance that is GRAS for a particular use in food is not a food additive, and may lawfully be utilized for that use without FDA review or approval. Currently, a GRAS determination may be made when the manufacturer or user of a food substance evaluates the safety of the substance and the views of qualified experts and determines that the use of the substance is GRAS. This approach is commonly referred to as “GRAS self-determination” or “independent GRAS determination.”

Other substances that are GRAS may be identified in FDA regulations in one of two ways. Following the passage of the 1958 Food Additives Amendment, we established in our regulations a list of food substances that, when used as indicated, are considered GRAS. We made clear that this was not a comprehensive list. This list (commonly referred to as the “GRAS list”) now appears at 21 CFR part 182. Thereafter, in 1972, we established the GRAS affirmation process through which we affirmed, through notice and comment rulemaking, the GRAS status of particular uses of certain substances in food. Regulations affirming the GRAS status of certain substances appear at 21 CFR parts 184 and 186. (As a general matter, we no longer affirm the GRAS status of substances through notice-and-comment rulemaking. In April 1997, we proposed to replace the voluntary GRAS affirmation petition process with a voluntary GRAS notification program, which would not involve rulemaking (62 FR 18938 (April 17, 1997)). At the time of the proposal, we initiated a pilot of the GRAS notification program, which continues to function. A firm may voluntarily submit information on a GRAS self-determination to FDA for review through the GRAS notification program, but is not required to do so.)

FDA received numerous comments on our tentative determination. Many related to the GRAS standard and what is needed to demonstrate that a substance is not GRAS. Many comments agreed with our determination that there is not a consensus among qualified experts that PHOs are safe for use in human food. However, there were also many comments that disagreed with FDA's tentative determination and stated that we did not adequately demonstrate that PHOs are not GRAS.

(Comment 3) Some comments stated that FDA must show a "severe conflict" among experts about the safety of a substance in order to determine that PHOs are not GRAS.

(Response) FDA disagrees that "severe conflict" is the relevant standard. As discussed in section III.A, general recognition of safety does not exist if there is a lack of consensus among qualified experts that the use of a substance is safe. We have considered all available information and determined that there is no longer a consensus among qualified experts that PHOs are safe for human consumption. To the extent there is disagreement among qualified experts about the safety of PHOs for human consumption, this genuine dispute regarding safety precludes a finding of GRAS.

(Comment 4) Some comments focused on the idea that it may be possible to establish a threshold below which PHOs may be safely used in the food supply. One comment argued that there is no consensus among experts that PHOs are unsafe below some low threshold level of use.

(Response) As discussed later in section IV.B.1, FDA does not agree that such a threshold has been identified based on the available science. Importantly, even if such a threshold could be identified, this alone would not meet the requirement of "general recognition" for uses below the threshold without there also being consensus among qualified experts that

uses below the threshold are safe. (See United States v. 7 Cartons, 293 F. Supp. 660, 663 (S.D. Ill. 1968) (“an inference that safety might be shown by scientific testing and procedures” is insufficient as a matter of law to demonstrate general recognition of safety), affirmed in relevant part, 424 F.2d 1364 (7th Cir. 1970).) FDA has no basis to conclude that there is any such consensus. FDA has previously revoked GRAS status under similar circumstances (51 FR 25021 at 25023, July 9, 1986; revoking GRAS status of sulfiting agents on fruits and vegetables intended to be served or sold raw to consumers; explaining that it was not possible to set a threshold for safe use based on available information). Moreover, we need not determine that there is a consensus that low level uses are unsafe to find that PHOs are not GRAS at low levels; we need only determine that based on available scientific evidence there is not a consensus among qualified experts that such uses are safe, as we do here. We acknowledge that scientific knowledge advances and evolves over time. We encourage 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 are establishing a compliance date of June 18, 2018 for this order to allow time for such petitions and their review.

(Comment 5) One comment stated that FDA must demonstrate that each and every PHO, and every use of PHOs, is not safe.

(Response) FDA disagrees. FDA need not demonstrate that PHOs are unsafe to determine that they are not GRAS, only that there is a lack of consensus among qualified experts regarding their safety. In addition, our consideration of PHOs as a class is justified because the available, relevant scientific evidence demonstrates an increased risk of coronary heart disease (CHD) attributable to trans fat (see section VI.B); PHOs are the primary dietary source of IP-

TFA; and there is a lack of consensus among qualified experts that PHOs are safe for use in food at any level.

(Comment 6) Some comments stated that, by determining that the use of PHOs are not GRAS because they contain a nutrient that increases risk of CHD, FDA would be calling into question the regulatory status of other food sources of trans fat.

(Response) FDA disagrees. As noted in section II, this order does not apply to ingredients that contain naturally occurring trans fat (such as those ingredients derived from ruminant sources), fully hydrogenated oils, or edible oils that contain IP-TFA as an impurity. FDA has considered the available information and concluded that there is a lack of consensus among qualified experts that PHOs, as the primary dietary source of IP-TFA, are safe for use in human food. We may determine that the use of an artificial substance is not GRAS without necessarily making the same determination about naturally-occurring versions of the substance. (See, e.g., 35 FR 7414 (May 13, 1970) (Rescinding letters that had expressed opinions that certain uses of glycine and its salts are GRAS, and stating that such added substances are no longer GRAS in human food); 37 FR 6938 (April 6, 1972) (Amino Acids in Food for Human Consumption; Proposed Conditions of Safe Use in Food and Deletion From GRAS List) (“[T]he mere natural presence of an amino acid in unprocessed foods in free or combined (as protein) form does not qualify it as safe for addition in a pure form as a component of a formulated or processed food”), 38 FR 20036 (July 26, 1973) (Amino Acids in Food for Human Consumption; Conditions of Safe Use in Food and Deletion From GRAS List); 47 FR 22545 (May 25, 1982) (Cinnamyl Anthranilate; Proposed Prohibition of Use in Human Food) (acknowledging “the presence of other cinnamyl and anthranilate derivatives naturally in food and in natural

substances used to flavor food” but proposing to prohibit only cinnamyl anthranilate); 50 FR 42929 (October 23, 1985) (Cinnamyl Anthranilate; Prohibition of Use in Human Food)).

(Comment 7) One comment stated that Congress, through the Nutrition Labeling and Education Act of 1990 (NLEA) (Pub. L. 101-535), prescribed labeling as the sole vehicle for achieving the nutritional policy objective of shifting dietary patterns to reduce the risk of multifactorial chronic diseases such as CHD. The comment argued that FDA’s use of its food additive authority with respect to PHOs and their effect on risk of CHD is not within FDA’s legal authority. Some comments characterized the tentative determination as a new approach or a change in interpretation, arguing that FDA has not previously addressed health concerns related to nutrient intake through the FD&C Act’s food additive provisions. In support of the argument that FDA has changed its interpretation of the applicability of the food additive provisions of the FD&C Act, one comment cited a statement by FDA in rulemaking regarding health claims that “where the only safety issue is an increased risk of chronic disease from excessive consumption, the safety provisions of the act would not provide regulatory sanctions against such components of food, at least if they have not been added to foods” (58 FR 2478 at 2490 (January 6, 1993)).

(Response) FDA disagrees with these comments. FDA may properly address such health risks using the food additive authorities in the FD&C Act (sections 201(s), 409, and 402(a)(2)(C) of the FD&C Act). The broad language of the food additive definition in section 201(s) of the FD&C Act covers “any substance” added to food, including nutrients. Nothing in the FD&C Act or its legislative history suggests that the food additive definition should be interpreted in a way that limits its applicability as the comment suggests. On the contrary, the legislative history of the Food Additives Amendment of 1958 (Pub. L. 85-929) emphasizes the broad applicability of sections 201(s), 409, and 402(a)(2)(C) of the FD&C Act, which apply to

“any substances the ingestion of which reasonable people would expect to produce not just cancer but any disease or disability” (S. Rep. No. 2422, at 11 (1958), as reprinted in Vol. 14, Legislative History of the Food, Drug & Cosmetic Act and its Amendments, at 923 (1979)). In fact, we have previously taken action regarding health risks related to nutrients using these authorities (55 FR 50777 (December 10, 1990) (determining certain Vitamin K Active Substances not GRAS); and 38 FR 20036 (July 26, 1973) (establishing conditions of safe use for amino acids for nutritive purposes and deleting them from GRAS list)). We also have previously applied these authorities to substances presenting increased health risks related to chronic multifactorial diseases, such as cancer (50 FR 42929 (October 23, 1985) (prohibiting use of cinnamyl anthranilate in food); and 34 FR 17063 (October 21, 1969) (prohibiting use of cyclamates in food)).

With respect to the comment citing a statement from a final rule on health claims, FDA does not agree that this statement shows any change in FDA’s position, as it was explicitly limited to situations that did not meet the food additive definition because the components discussed “have not been added to foods.” The statement is consistent with FDA’s current understanding of the law.

Moreover, FDA disagrees with the argument that FDA must address health risks related to PHOs through food labeling requirements rather than through the food additive provisions of the FD&C Act. The NLEA amended the FD&C Act to provide, among other things, for certain nutrients and food components to be included in nutrition labeling. Section 403(q)(2)(A) and (q)(2)(B) (21 U.S.C. 343(q)(2)(A) and (q)(2)(B)) of the FD&C Act state that the Secretary of Health and Human Services (the Secretary) (and, by delegation, FDA) can, by regulation, add or delete nutrients included in the food label or labeling if he or she finds such action necessary to

assist consumers in maintaining healthy dietary practices. We have used this authority to require labeling of trans fat content (68 FR 41434 (July 11, 2003); see also § 101.9(c)(2)(ii) and § 101.36(b)(2)(i)) (21 CFR 101.36(b)(2)(i)). Although we may further address trans fat through labeling requirements in the future, labeling is not the only method by which we may address health risks related to trans fats, and more specifically health risks related to PHOs, the primary dietary source of IP-TFA. Nothing in the NLEA suggested that its passage limited the preexisting food additive provisions in the FD&C Act, or that the food additive provisions did not apply to nutrients and chronic multifactorial disease under appropriate circumstances. On the contrary, as the comment noted, the NLEA contained a clause stating that “[t]he amendments made by this Act shall not be construed to alter the authority of the Secretary of Health and Human Services... under the [FD&C Act]” (NLEA section 9).

The FD&C Act’s nutrition labeling and food additive provisions are two different kinds of authority, with different standards, and we may choose among available approaches to a public health problem when the FD&C Act provides multiple options. See, e.g., Chevron U.S.A. Inc. v. Natural Resources Defense Council, 467 U.S. 837, 865-6 (1984) (“While agencies are not directly accountable to the people, the Chief Executive is, and it is entirely appropriate for this political branch of the Government to make such policy choices -- resolving the competing interests which Congress itself either inadvertently did not resolve, or intentionally left to be resolved by the agency charged with the administration of the statute in light of everyday realities”); United States v. Mead Corp., 533 U.S. 218, 227 (2001) (“agencies charged with applying a statute necessarily make all sorts of interpretive choices”). There is no “conflict” between the FD&C Act’s nutrition labeling provisions and food additive provisions as the comment suggests. It is also worth noting that we have previously determined that a use of a

substance is not GRAS while rejecting a labeling-based approach to the health risks presented by that use (51 FR 25021 (July 9, 1986) (final rule revoking GRAS status of sulfiting agents on fruits and vegetables intended to be served or sold raw to consumers); and 50 FR 32830 (August 14, 1985) (proposal to revoke GRAS status of sulfiting agents on fruits and vegetables intended to be served or sold raw to consumers)).

(Comment 8) Some comments stated that the expert panels we cited in the tentative determination (i.e., the Institute of Medicine/National Academy of Sciences (IOM/NAS), American Heart Association, American Dietetic Association, World Health Organization, Dietary Guidelines Advisory Committee, and the FDA Food Advisory Committee Nutrition Subcommittee) were not experts qualified by scientific training and experience to evaluate the safety of substances in food. The comments also stated that these expert panels were not convened for the purposes of evaluating the safety of PHOs and did not make determinations regarding the GRAS status of PHOs. Therefore, the comments argued that the conclusions of these panels do not demonstrate a lack of consensus among qualified experts that PHOs are GRAS.

(Response) FDA disagrees with these comments. The expert panels we cited were composed of scientists qualified by relevant training and experience to review literature on trans fat consumption, because of their nationally recognized and established expertise in the area of food and nutrition. For example, the Food and Nutrition Board at IOM/NAS is a recognized national resource for recommendations on health issues, and the Dietary Guidelines Advisory Committee members are nationally recognized experts in nutrition and health. These panels' evaluations and conclusions raised significant questions about the safety of trans fat, thus showing that there is no consensus among qualified scientific experts that PHOs are safe,

because PHOs are the primary dietary source of IP-TFA. The safety information reviewed by the panels is further discussed in section IV.B.2. We consider that the conclusions of the panels demonstrate that there is a “lack of the proper reputation... for safety of the food additive among the appropriate experts.” Coli-Trol 80, 518 F.2d at 746. Further, whether the panels were convened specifically to make a GRAS determination is irrelevant; the purpose of the panels was to review the available data on health risks associated with consumption of trans fat. Moreover, the expert panel conclusions are not the only evidence upon which we rely for this determination, and conclusions of an expert panel are not required to establish general recognition of safety or its absence.

(Comment 9) Several comments stated that the expert panels we cited considered nutritional science and not safety.

(Response) FDA disagrees that the panels were not considering safety data; panels were considering data from controlled trials and observational studies on trans fat consumption that showed adverse effects on risk factors (e.g., effects on cholesterol) and increased risk of CHD (see section IV.B.2 for further discussion on expert panel reviews). As discussed in more detail in section III.A, FDA regulations define “safe” as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use” (§ 170.3(i)), and data showing a potential relationship between a nutrient (or any other substance added to food) and disease are safety data. Studies reviewed by expert panels showed that trans fatty acids cause significant health risks. Such studies are safety data.

(Comment 10) One comment stated that FDA should hold the manufacturer initially introducing the food or ingredient into interstate commerce responsible for compliance with a

determination that PHOs are not GRAS, and that distributors should not be responsible for determining whether foods they merely distribute contain PHOs.

(Response) Although we are mindful of the need to focus our enforcement efforts, those needs do not change the underlying law or FDA's legal authority. Food that is adulterated may be subject to seizure and distributors, manufacturers, and other parties responsible for such food may be subject to injunction. We recognize that manufacturers who have previously added PHO to food, rather than other parties such as distributors who merely receive and sell finished foods, are the members of the food industry who will be most directly affected by this order, and we intend to focus our outreach and enforcement resources accordingly. However, we remind distributors and other members of the food industry that they have an obligation to ensure that the food they manufacture, distribute, sell, or otherwise market complies with the FD&C Act.

(Comment 11) Some comments requested that FDA take a position regarding the effect of this order on state and local laws regarding PHOs.

(Response) There is no statutory provision in the FD&C Act providing for express preemption of any state or local law prohibiting or limiting use of PHOs in food, including state or local legislative requirements or common law duties. As with any Federal requirement, if a State or local law requirement makes compliance with both Federal law and State or local law impossible, or would frustrate Federal objectives, the State or local requirement would be preempted. See Wyeth v. Levine, 555 U.S. 555 (2009); Geier v. American Honda Co., 529 U.S. 861 (2000); English v. General Electric Co., 496 U.S. 72, 79 (1990), Florida Lime & Avocado Growers, Inc., 373 U.S. 132, 142-143 (1963); Hines v. Davidowitz, 312 U.S. 52, 67 (1941). We decline to take a position regarding the potential for implied preemptive effect of this order on any specific state or local law; as such matters must be analyzed with respect to the specific

relationship between the state or local law and the federal law. FDA believes, however, that state or local laws that prohibit or limit use of PHOs in food are not likely to be in conflict with federal law, or to frustrate federal objectives.

B. Prior Sanctions

We stated in our tentative determination that we were not aware that FDA or U.S. Department of Agriculture (USDA) had granted any explicit approval for any use of PHOs in food prior to the 1958 Food Additives Amendment to the FD&C Act, and requested comments on whether there was knowledge of an applicable prior sanction for the use of PHOs in food (78 FR 67169 at 67174). We received various comments on this topic. We are not making a determination regarding the existence of any prior sanctions for uses of PHO in this order. This order is limited to our determination regarding the GRAS status of PHOs. We intend to address any claims of prior sanction in a future action.

C. Procedural Requirements

Under 5 U.S.C. 554(e) (section 5(d) of the Administrative Procedure Act (APA)), an agency, “in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty.” The APA defines “order” as “the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rulemaking but including licensing” (5 U.S.C. 551(6)). The APA defines “adjudication” as “agency process for the formulation of an order” (5 U.S.C. 551(7)).

FDA’s regulations, consistent with the APA, define “order” to mean “the final agency disposition, other than the issuance of a regulation, in a proceeding concerning any matter...” (§ 10.3(a) (21 CFR 10.3(a)). Our regulations also define “proceeding and administrative proceeding” to mean “any undertaking to issue, amend, or revoke a regulation or order, or to take

or not to take any other form of administrative action, under the laws administered by the Food and Drug Administration” (§ 10.3(a)). Moreover, our regulations establish that the Commissioner may initiate an administrative proceeding to issue, amend, or revoke an order (21 CFR 10.25(b)).

FDA’s regulations also set forth a process by which we, on our own initiative or on the petition of an interested person, may determine that a substance is not GRAS. Specifically, FDA may initiate this process by issuing a notice in the Federal Register proposing to determine that a substance is not GRAS and is a food additive subject to section 409 of the FD&C Act (§ 170.38(b)). The notice must allow a period of 60 days for comment. If, after review of comments, FDA determines that there is a lack of convincing evidence that a substance is GRAS or is otherwise exempt from the definition of a food additive in section 201(s) of the FD&C Act, FDA will publish a notice thereof in the Federal Register (§ 170.38(b)(3)). Such a notice “shall provide for the use of the additive in food or food contact surfaces as follows: (1) It may promulgate a food additive regulation governing use of the additive[;] (2) It may promulgate an interim food additive regulation governing use of the additive[;] (3) It may require discontinuation of the use of the additive[;] (4) It may adopt any combination of the above three approaches for different uses or levels of use of the additive” (§ 170.38(c)).

On our own initiative, we began an administrative proceeding to formulate a 5 U.S.C. 554(e) declaratory order to remove uncertainty regarding the GRAS status of PHOs. Accordingly, we published a notice in the Federal Register, consistent with § 170.38(b), communicating our tentative determination that PHOs are no longer GRAS for any use in food, and allowed 60 days for comments (78 FR 67169 (November 8, 2013)). We later extended the comment period for an additional 60 days (78 FR 79701 (December 31, 2013)).

In the tentative determination, FDA noted that two PHOs had been affirmed by regulation as GRAS for use in food (78 FR 67169 at 67171; the partially hydrogenated versions of low erucic acid rapeseed oil (LEAR oil; § 184.1555(c)(2)) and menhaden oil (§ 184.1472(b)). We also noted that the nature of some of the products for which there are standards of identity is such that PHOs historically have been used in their manufacture in conformance with those standards (78 FR 67169 at 67171). However, we also noted that no food standard of identity requires the use of PHOs and, therefore, industry's ability to comply with any standard would not be prevented by a change in the regulatory status of PHOs. As discussed in section III.B, two standards of identity explicitly mention PHOs in allowing partially hydrogenated vegetable oil as an optional ingredient; the standards of identity for peanut butter (§ 164.150 (21 CFR 164.150)) and canned tuna (§ 161.190 (21 CFR 161.190)). Because these standards do not require the use of PHOs, industry's ability to comply with them would not be prevented by a change in the regulatory status of PHOs. In addition, our labeling regulations explicitly address ingredient designations for PHOs (§ 101.4(b)(14) (21 CFR 101.4(b)(14))).

This final determination is a 5 U.S.C. 554(e) declaratory order regarding the status of PHOs. Consistent with § 170.38(b)(3), we have reviewed the comments received and determined that there is a lack of convincing evidence that PHOs are GRAS. Thus, consistent with § 170.38(c)(3), we are publishing a notice thereof in the Federal Register that requires discontinuation of the use of these additives. Moreover, we are providing advance notice of our intention to undertake rulemaking with respect to the uses of PHOs explicitly permitted for use by regulation and other conforming changes.

(Comment 12) Some comments argued that FDA must determine the GRAS status of PHOs through notice-and-comment rulemaking.

(Response) FDA agrees that we must conduct rulemaking to revise §§ 184.1555(c)(2) and 184.1472(b), which explicitly permit the use of partially hydrogenated LEAR oil and partially hydrogenated menhaden oil, respectively. FDA will also consider taking further action to revise regulations regarding the standards of identity for peanut butter (§ 164.150(c)) and canned tuna (§ 161.190(a)(6)(viii)), the regulation regarding ingredient designations for PHOs (§ 101.4(b)(14)), and nutrition labeling regulations regarding trans fats (§§ 101.9(c)(2)(ii) and 101.36(b)(2)(i)). We note that although trans fat does occur naturally in some product groups such as dairy foods, it is only likely to be present at levels at or above 0.5 g per serving in products containing PHOs.

We do not agree that we must determine the GRAS status of PHOs generally via rulemaking. FDA may properly make such a determination in an order, as we have chosen to do here. This is not the first time FDA has issued a declaratory order when determining that a substance is not GRAS and is a food additive. See 55 FR 50777, 50778 (Declaratory Order regarding Vitamin K Active Substances in Animal Food, issued under 21 CFR 570.38, the regulation for animal food that parallels § 170.38 for human food).

We have authority to administer the statutory provisions of the FD&C Act that are most relevant to this determination, namely, are sections 201(s), 402(a)(2)(C), and 409 of the FD&C Act. Section 201(s) of the FD&C Act defines a food additive, in part, as a substance that is not GRAS, and section 402(a)(2)(C) of the FD&C Act establishes that food bearing or containing a food additive that is unsafe within the meaning of section 409 of the FD&C Act is adulterated. Section 409 of the FD&C Act establishes that a food additive is unsafe for the purposes of section 402(a)(2)(C) of the FD&C Act (and therefore adulterated) unless certain criteria are met, such as conformance with a regulation prescribing the conditions under which the additive may

be safely used. Section 409 of the FD&C Act also sets forth a process by which we administer the review of food additive petitions and may establish regulations prescribing conditions of safe use for such additives. Thus, we have explicit statutory authority to review, approve, and deny food additive petitions.

Because it is necessary to determine whether the use of a substance is GRAS as part of identifying it as a food additive, it is implicit in this statutory structure that we also have the authority to determine whether the use of a substance is, or is not, GRAS. The statute does not explicitly provide the procedure we must use to make such determinations. Thus, we may choose to use either rulemaking or adjudication. “The choice between rule-making or declaratory order is primarily one for the agency regardless of whether the decision may affect policy and have general prospective application.” (See Viacom v. FCC, 672 F.2d 1034, 1042 (2nd Cir. 1982). See also SEC v. Chenery, 332 U.S. 194, 203 (1947); NLRB v. Wyman-Gordon Co., 394 U.S. 759 (1969); NLRB v. Bell Aerospace Co., 416 U.S. 267, 294 (1974); Almy v. Sebelius, 679 F.3d 297, 303 (4th Cir. 2012); City of Arlington, Texas v. FCC, 133 S. Ct. 1863, 1874 (2013); Qwest Servs. Corp. v. FCC, 509 F.3d 531, 536-37 (D.C. Cir. 2007) (“Most norms that emerge from a rulemaking are equally capable of emerging (legitimately) from an adjudication, and accordingly agencies have very broad discretion whether to proceed by way of adjudication or rulemaking” (internal citations and quotations omitted)).

Determining that PHOs are no longer GRAS for use in human food in a declaratory order issued as a product of informal adjudication is well within FDA’s discretion under the FD&C Act and the APA. Whether PHOs are GRAS for use in human food is a “concrete and narrow question[] of law the resolution[] of which would have an immediate and determinable impact on specific factual scenarios” (City of Arlington v. FCC, 668 F.3d 229, 243 (5th Cir. 2012)). (See

also Qwest Servs. Corp., 509 F.3d at 536-37; Chisholm v. FCC, 538 F.2d 349, 364-66 (D.C. Cir. 1976); American Bar Association, A Guide to Federal Agency Adjudication 8 (Jeffrey B. Litwak, ed., 2012) (Agency order to withdraw certain food from the market, which has particular applicability and future effect, provided as an example of adjudication)). We are issuing this declaratory order to remove uncertainty as to the status of PHOs as food additives. The order is a product of an informal adjudication that included notice to affected parties via publication of the tentative determination in the Federal Register and an opportunity for affected parties to be heard by submitting comments to the Agency. Such procedures are appropriate for the formulation of declaratory orders. (See, e.g., Weinberger v. Hynson, Westcott and Dunning Inc., 412 U.S. 609, 626 (1973); American Airlines v. Dep't. of Transportation, 202 F.3d 788, 796-797 (5th Cir. 2000). See also Lubbers, Jeffrey S. and Blake D. Morant, A Reexamination of Federal Agency Use of Declaratory Orders, 56 Admin. L. Rev. 1097, 1112-1114 (2004) and cases cited therein). Moreover, “adjudicatory decisions are not subject to the APA’s notice-and-comment requirements” (Blanca Telephone Co. v. FCC, 743 F.3d 860 (D.C. Cir. 2014)).

Issuance of a declaratory order is also consistent with our regulations (§ 170.38(c)(3)), which provide that we may publish a notice in the Federal Register that requires discontinuation of the use of these additives, and do not specify that we must do so through rulemaking. Notably, other subsections of § 170.38(c) mention promulgation of regulations, but § 170.38(c)(3), providing for prohibition of use, does not. Moreover, when we make a determination under § 170.38 that a substance is not GRAS, we must take one (or a combination) of the actions listed in § 170.38(c). See Heterochemical Corp. v. FDA, 741 F. Supp. 382, 384 (E. D. N.Y. 1990).

The purpose of a declaratory order is “to develop predictability in the law by authorizing binding determinations which dispose of legal controversies without the necessity of any party’s acting at his peril upon his own view” (U.S. Department of Justice, Attorney General’s Manual on the Administrative Procedure Act (1947) at 59, reprinted in Federal Administrative Procedure Sourcebook (William F. Funk et al. ed., ABA Section of Administrative Law and Regulatory Practice 3rd ed. 2000)). Members of industry are not, as some comments suggested, faced with a choice between complying with a non-binding statement of policy and facing enforcement action. This is not a statement of policy. This declaratory order has the force and effect of law.

(Comment 13) Some comments assumed that this order was a statement of policy, and, on that basis, argued that this action violates Due Process requirements.

(Response) As explained in our response to comment 10, that assumption is incorrect. Further, FDA’s order and the process used in its formulation raise no Due Process concern.

(Comment 14) Some comments argued that FDA did not conduct a full Regulatory Impact Analysis in issuing the tentative determination.

(Response) As discussed previously in this section, this final determination is a declaratory order issued as the result of informal adjudication to remove uncertainty regarding the status of PHOs. We have prepared a memorandum (Ref. 17) updating our previous estimate of economic impact published in the November 2013 notice, using information available to us as well as information we received during the comment period. See discussion in section VII. Further, we have stated our intention to conduct rulemaking regarding uses of PHOs in our existing regulations, and such rulemakings will be subject to the procedural requirements pertaining to rulemaking.

(Comment 15) One comment stated that FDA must provide a more detailed justification for this action than what was provided in the tentative determination because it is a change in FDA's position regarding PHOs and industry has a substantial reliance interest in the GRAS status of PHOs.

(Response) In the tentative determination (78 FR 67169 at 67172) and in this order, FDA has explained the factual findings supporting this action in detail. In section IV.B, we describe how the scientific evidence, and consensus among qualified experts regarding the safety of PHOs, has changed over time. We are not changing our interpretation of the GRAS standard or the relevant regulations. We are determining that PHOs are no longer GRAS by applying the GRAS standard to current scientific evidence and the views of qualified experts about the safety of PHOs. Moreover, reliance interests are implicated whenever FDA makes a determination that removes a substance from the food supply that has been previously used in food. FDA is aware of such concerns; however, the statutory standard for GRAS does not allow FDA to consider the extent to which industry has relied on GRAS uses of a substance. We encourage industry to submit food additive petitions under section 409 of the FD&C Act if industry believes that it is possible to establish, by regulation, safe conditions of use of PHOs. We are establishing a compliance date of June 18, 2018 for this order to allow time for submission of such petitions and their review and approval, if applicable requirements are met.

IV. Discussion of Scientific Issues, and Related Comments With FDA Responses

A. Intake Assessment

In the November 2013 notice, we discussed dietary intake of trans fat from PHOs, estimated in 2010 and updated in 2012 (78 FR 67169 at 67171). The intake assessment was done for four reasons: (1) To determine the impact of the 2003 labeling rule and subsequent

reformulations; (2) to assist in our review of the citizen petitions, which are discussed in section V; (3) to consider strategies for further trans fat reduction, if warranted; and (4) to better understand the current uses of PHOs and identify products that still contain high levels of trans fat. Our determination regarding the GRAS status of PHOs relies on an analysis of whether PHOs meet the GRAS standard based on available scientific evidence; the intake assessment was not the basis for this determination.

In 2012, we estimated the mean trans fat intake from the use of PHOs to be 1.0 grams per person per day (g/p/d; 0.5 percent of energy based on a 2,000 calorie diet¹) for the U.S. population aged 2 years or more. We also estimated intake for high-level consumers (represented by intake at the 90th percentile), as well as a “high-intake” scenario that assumed consumers consistently chose products with the highest trans fat levels. We received a number of comments on our intake assessment, including comments on assumptions, methodology, and recommendations for future studies.

(Comment 16) One comment challenged FDA’s statement that intake of trans fat did not significantly change between 2010 and 2012. The comment indicated that the intake of trans fat from the use of PHOs decreased by roughly 23% in that time period due to significant reformulation efforts by the food industry.

(Response) FDA agrees that a comparison of the assessments from 2010 and 2012 demonstrates that reformulation has occurred and intake has decreased. While the intake estimates did show a 23 percent decrease in trans fat intake between 2010 and 2012 (1.3 g/p/d to 1.0 g/p/d), this change is small compared to the 3.3 g/p/d difference between FDA’s intake estimate in the 2003 trans fat labeling final rule of 4.6 g/p/d and the 2010 estimate of 1.3 g/p/d (about a 72 percent decrease). This was the context for the statement in the tentative

¹ $(1.0 \text{ g/p/d} \times 9 \text{ kcal/g} \times 100)/2,000 \text{ kcal/d} = 0.5\% \text{ of energy.}$

determination that, “We do not consider this to be a significant change in the overall dietary intake of trans fat since 2010. However, it suggests a continued downward trend in the dietary intake of trans fat.”

(Comment 17) Many comments stated that a substantial number of products have been reformulated since the 2012 intake assessment and that we should revise our intake assessment for trans fat before issuing our final determination on the GRAS status of PHOs.

(Response) FDA agrees that reformulation efforts by industry are continuing. However, the 2012 intake assessment was intended to be a snapshot in time and was based on products containing PHOs that were in the market at that time, and was done for the reasons described previously in this section. Given the evidence FDA has reviewed and our determination that PHOs are not GRAS for any use in human food, an updated intake assessment for trans fats from PHOs is not needed at this time. Our determination that PHOs are not GRAS for use in human food does not rely on the intake assessment.

(Comment 18) Some comments stated that FDA should not use the “high intake scenario” as justification for a determination that PHOs are not GRAS. Related comments stated that the intake for the highest level consumers should be determined directly rather than using worst-case scenario assumptions.

(Response) FDA disagrees that the high intake assessments provide justification for our determination regarding the GRAS status of PHOs; the determination is based on our assessment of whether any use of PHOs in human food meets the GRAS standard, based on available scientific evidence. Our determination did not rely on the intake assessment.

(Comment 19) Several comments stated that FDA’s estimate did not calculate intake from animal products that contain trans fat, and that FDA should update the intake assessment to

include the intake of total trans fat from both ruminant sources and IP-TFA. The comments noted this was necessary to understand if dietary recommendations are being met. One comment indicated that a recent publication suggests that the intake of trans fat from ruminant sources may be decreasing, thereby indicating a more inclusive review of dietary intake of trans fat is warranted. Another comment stated that we did not consider the cumulative effect of trans fat because it did not present data on intake from all sources, including ruminant TFA.

(Response) Our study was designed to assess trans fat intake from the use of PHOs, because they are the primary source of IP-TFA, and IP-TFA was the focus of the intake assessment. As stated in our tentative determination (78 FR 67169 at 67172), the IOM's recommendation is that trans fat consumption should be kept as low as possible while consuming a nutritionally adequate diet, recognizing that trans fat occurs naturally in meat and dairy products from ruminant animals and that naturally-occurring trans fat is unavoidable in ordinary, non-vegan diets without significant dietary adjustments that may introduce undesirable effects. Therefore, our intake assessment focused only on trans fat from the use of PHOs, the primary dietary source of IP-TFA, in which trans fat is produced intentionally and is an integral component.

(Comment 20) One comment urged FDA to reevaluate the intake of trans fat using the most recent National Health and Nutrition Examination Survey (NHANES) data. The comment suggested that the intake of trans fat would be lower if the more recent NHANES data were used because the mandatory labeling rule for trans fat became effective on January 1, 2006.

(Response) While the 2003-2006 NHANES food consumption data were used in the 2010 and 2012 intake assessments, the levels of trans fat in the food products were determined based on products that were available in the market from 2009 to 2012, therefore capturing trans

fat reductions due to product reformulation as a result of the regulation in § 101.9(c)(2)(ii) (effective in 2006) requiring declaration of the trans fat content of food in the nutrition label. The consumption of products in the food categories in which PHOs are used would not be expected to change significantly over a few years because for the most part, foods tend to be commonly consumed with little or no change in consumption patterns over short periods of time. Further, we compared the typical intake of trans fat using the 2003-2006 and 2003-2008 NHANES food consumption data and found that there were no significant differences in the intakes (Ref. 16).

(Comment 21) Several comments suggested that using a value of 0.4 g trans fat per serving for foods that declared 0 g trans fat on the label, but contained a PHO was an overestimation of intake. One comment stated that this assumption represents 40% of the estimated daily intake of 1.0 g/p/d.

(Response) FDA disagrees with the comments. For most of the food products that declared 0 g trans fat on the label, but contained a PHO, a level based on analytical data was used. A value of 0.4 g trans fat/serving was used for only 2 percent of all of the food codes included in the intake assessment (Ref. 16). The value of 0.4 g is the amount of trans fat estimated to be in in the food(s) that corresponds to a given food code that was used in the intake assessment, and does not represent a percentage of total estimated intake. As a result, we do not expect that using a lower value would significantly affect the overall estimated intake of trans fat from the use of PHOs. The use of 0.4 g trans fat/serving was reserved for those cases where no other information was available (i.e., analytical data or an appropriate surrogate). Furthermore, while numerically 0.4 g is 40 percent of 1.0 g, it is not appropriate to compare these two parameters. Many factors (i.e., the amount of the particular food consumed, the percent of the

population consuming the given food, and the level of trans fat in the particular food) were used to derive the overall estimated trans fat intake.

(Comment 22) One comment suggested that American Oil Chemists Society (AOCS) methods should be used for the intake assessment instead of the AOAC method 996.06 since the AOAC method is outdated and has not undergone validation.

(Response) FDA disagrees. This AOAC method is widely used by industry and other international organizations as a method for determining the trans fat content in food products. Therefore, we considered the AOAC method to be appropriate for analyzing food samples for the purposes of our intake assessment. Our choice of the AOAC method is not intended to imply that industry must use this method to analyze food products.

(Comment 23) Two comments indicated that a new intake assessment should be performed using modeling to explore potential unintended consequences of decreasing the trans fat intake given the possible replacements for trans fat (e.g., saturated fat, carbohydrate) and their impact on CHD risk.

(Response) The safety of other substances that are possible replacements for PHOs is outside the scope of this order. However, although we have not updated the intake assessment since 2012, we have used this intake assessment to calculate the expected impact of this order on CHD events, taking into account possible replacements for PHOs (see section IV.B for detailed discussion).

(Comment 24) One comment noted that FDA did not examine the use of each PHO and the probable consumption of each use.

(Response) FDA disagrees that we need to examine the intake of each PHO individually; the intent of the intake estimate was to evaluate the overall intake of trans fat from the use of all

PHOs for the purposes described previously in this section. Estimating trans fat intake from individual PHOs would be an impractical undertaking, and was not necessary for the purposes of the intake assessment.

(Comment 25) Two comments stated that intake should be evaluated based on the presumption that all products with PHOs as an ingredient contain trans fat at a specified level (e.g., 0.2 g/serving or per reference amount customarily consumed). These comments suggested that such an assessment could provide support for an alternative approach such as setting an allowable level of trans fat in foods.

(Response) Because we have concluded that PHOs are no longer GRAS, evaluating intake for alternative approaches, such as setting an allowable level of trans fat in foods, is not planned at this time.

B. Safety

In the Federal Register of November 17, 1999 (64 FR 62746), we issued a proposed rule entitled “Food Labeling: Trans Fatty Acids in Nutrition Labeling, Nutrient Content Claims, and Health Claims.” The proposed rule would require that trans fat content be provided in nutrition labeling, and concluded that dietary trans fats have adverse effects on blood cholesterol measures that are predictive of CHD risk, specifically low-density lipoprotein cholesterol (LDL-C) levels (64 FR 62746 at 62754). In the Federal Register of July 11, 2003 (68 FR 41434), we issued a final rule (the July 2003 final rule) amending the labeling regulations to require declaration of trans fat content of food in the nutrition label of conventional foods and dietary supplements (68 FR 41434). In the July 2003 final rule, we cited authoritative reports that recommended limiting intake of trans fat to reduce CHD risk (68 FR 41434 at 41442).

In the November 2013 notice containing our tentative determination that PHOs are no longer GRAS for any use in human food, we summarized findings reported in the literature since 2003, when we had last reviewed the adverse effects of dietary trans fat in support of the July 2003 final rule (68 FR 41434 at 41442 through 41449). We noted that since 2003, both controlled feeding trials and prospective observational studies published on trans fat consumption have consistently confirmed the adverse health effects of trans fat consumption on risk factor biomarkers (e.g., serum lipoproteins including LDL-C) and increased risk of CHD (78 FR 67169 at 67172). We describe these two types of studies (controlled feeding trials and prospective observational studies) in further detail later in this section. We also cited a variety of different kinds of studies and review articles showing that, in addition to an increased risk of CHD, trans fat consumption (and, accordingly, consumption of food products containing PHOs) has also been connected to a number of other adverse health effects (id.). These effects included worsening insulin resistance, increasing diabetes risk, and adverse effects on fetuses and breastfeeding infants, such as impaired growth.

Since publication of the November 2013 notice, we re-reviewed key literature and expert panel reports published since the 1990s on the relationship between trans fat consumption and CHD risk (Ref. 18). Our review focused on the two main lines of scientific evidence linking trans fat intakes and CHD: (1) The effect of trans fat intake on blood lipids in controlled feeding trials, a type of randomized clinical trial; and (2) observational (epidemiological) studies of trans fat intake and CHD risk in populations. Additionally, we reviewed the conclusions of recent U.S. and international expert panels on the health effects of trans fat. As summarized in our review memorandum (Ref. 18), the scientific evidence, including combined analyses of multiple studies (meta-analyses), supports a progressive and linear cause and effect relationship between

trans fatty acid intake and adverse effects on blood lipids that predict CHD risk, including LDL-C, high-density lipoprotein cholesterol (HDL-C) and ratios such as total cholesterol (total-C)/HDL-C and LDL-C/HDL-C. The observational (epidemiological) studies demonstrating increased CHD risk associated with trans fat intake do not prove cause and effect, but the results are consistent with and supportive of the evidence from controlled feeding trials of the adverse effect of trans fatty acid intake on blood lipids that predict CHD risk. The consistency of the evidence from two different study methodologies provides strong support for the conclusion that trans fatty acid intake has a progressive and linear effect that increases the risk of CHD.

Risk factors are variables that correlate with incidence of a disease or condition. Risk factors include social and environmental factors in addition to biological factors. A biomarker is a characteristic that can be objectively measured and indicates physiological processes. A risk biomarker or risk factor biomarker is a biomarker that indicates a risk factor for a disease. In other words, it is a biomarker that indicates a component of an individual's level of risk for developing a disease or level of risk for developing complications of a disease (Ref. 19). LDL-C, HDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio are all currently considered to be risk biomarkers for CHD (Refs. 19, 20, 21, and 22). LDL-C is a risk factor biomarker that is also a surrogate endpoint for CHD; a "surrogate" is a validated predictor of CHD and can substitute for actual disease occurrence in a clinical trial (Refs. 19, 20, and 21). HDL-C, total-C/HDL-C and LDL-C/HDL-C are recognized as major risk factor biomarkers that, although they are not validated surrogate endpoints, are predictive of CHD risk (Refs. 19 and 22).

Effect of trans fat intake on blood lipids in controlled feeding trials. In controlled feeding trials, a type of randomized clinical trial, trans fatty acid intake increased LDL-C ("bad" cholesterol), decreased HDL-C ("good" cholesterol) and increased ratios of total-C/HDL-C and

LDL-C/HDL-C compared with the same amount of energy intake (calories) from cis-unsaturated fatty acids. Increases in LDL-C, total-C/HDL-C and LDL-C/HDL-C and decreases in HDL-C are adverse changes with respect to CHD risk. These adverse effects of trans fat intake on blood lipids are based on controlled feeding trials, a study design that is able to reveal cause and effect relationships between changes in trans fat intake and changes in blood lipids. In addition, increases in CHD risk with increases in LDL-C also demonstrate cause and effect. As described in our review memorandum (Ref. 18), combined analyses (meta-analyses) of multiple controlled feeding trials demonstrate a progressive and linear relationship between trans fatty acid intake and adverse effects on blood lipids including LDL-C, HDL-C, total-C/HDL-C and LDL-C/HDL-C. The meta-analyses describe consistent quantitative relationships between trans fat intake and blood lipids and show no evidence of a threshold below which trans fatty acids do not adversely affect blood lipids.

Observational (epidemiological) studies of trans fat intake and CHD risk in populations.

Epidemiology is the study of the distribution and causes of disease in human populations. Analytic epidemiology studies are those designed to test hypotheses regarding whether or not a particular exposure is associated with causing or preventing a specific disease outcome. In prospective observational (cohort) studies, subjects are classified according to presence or absence of a particular factor (such as usual dietary intake of trans fat) and followed for a period of time to identify disease outcomes (such as heart attack or death from CHD). Strengths of the prospective observational study design are that the time sequence of exposure and disease is clearly shown; exposures are identified at the outset of the study; and measurement of exposure is not affected by later disease status. Results of four major prospective studies, some with one or more updates during the followup period, consistently show higher trans fat intake associated

with increased CHD risk. The association is positive and progressive, with no indication of a threshold. A 2009 meta-analysis of the major prospective studies, based on almost 5,000 CHD events in almost 140,000 subjects, found that each additional 2 percent of energy intake from trans fat increased CHD risk by 23 percent compared with the same energy intake from carbohydrate.

Conclusions of recent U.S. and international expert panels on the health effects of trans fat. As described in our review memorandum (Ref. 18), international and U.S. expert panels, using additional scientific evidence available since 2002, have continued to recognize the positive linear trend between LDL-C and trans fat intake and the consistent association of trans fat intake and CHD risk in prospective observational studies. The panels have concluded that trans fats are not essential nutrients in the diet, and have recommended that consumption be kept as low as possible. Recommendations to avoid industrial trans fat intake have come from panels with both clinical and public health focus. Moreover, international and U.S. panels have expressed concern regarding population mean intakes of industrial trans fat intakes of 1 percent of energy and lower, recognizing that subgroups may be consuming relatively high levels.

Since publication of the November 2013 notice, we also conducted a systematic search of the peer-reviewed literature published since 2008 and summarized the findings (Ref. 23). The major human health endpoints evaluated for associations with trans fat intake reported in the literature included CHD, all-cause mortality, cardiovascular disease and stroke. Other human health endpoints addressed in our search included various types of cancer, metabolic syndrome and diabetes, and adverse effects on fertility, pregnancy outcome, cognitive function, and mental health. The literature search identified meta-analyses of published data; quantitative estimations to predict effects of replacing TFA in commercial products; cross-sectional, case-control and

prospective observational cohort studies; and randomized controlled trials, including controlled feeding trials. Regarding cardiovascular diseases, the results of the literature search (Ref. 23) are consistent with findings discussed in our November 2013 notice (78 FR 67169 at 67172).

Findings associated with higher TFA intakes included increased risk of CHD, adverse effects on biomarkers associated with CHD, and increased subclinical atherosclerosis. Some recent prospective observational studies also found associations between increased trans fat intake and increased risk of stroke, which was a new finding (Refs. 18 and 23). Further understanding of the apparent association between increased trans fat intake and increased risk of stroke requires additional research, such as whether the association may differ by age, sex, aspirin use, geographic region and other risk factors (Refs. 18, 23, and 24). For the association of trans fat intake with other human health effects, such as various types of cancer, metabolic syndrome and diabetes, and adverse effects on fertility, pregnancy outcome, cognitive function and mental health, the literature reports remained limited or inconclusive.

Since publication of the November 2013 notice, we also conducted a quantitative estimate of the potential health benefits expected to result from removal of IP-TFA from PHOs from the food supply (Ref. 25). We did this to analyze the expected public health benefit of removing PHOs from the food supply. We used four methods for estimating changes in CHD risk likely to result from replacement of IP-TFA: Method 1, based on effects of TFA on LDL-C, a validated surrogate endpoint biomarker for CHD, as shown through controlled feeding trials; Method 2, based on effects of TFA on LDL-C plus HDL-C, a major CHD risk factor biomarker, as shown through controlled feeding trials; Method 3, based on effects of TFA on total-C/HDL-C plus a combination of emerging CHD risk factor biomarkers (lipoprotein(a), apolipoproteinB/apolipoproteinA1 and C-reactive protein), as shown through controlled feeding

trials; and Method 4, based on association of TFA with CHD risk as shown through prospective observational studies. Methods 1 and 2 were also used by FDA in analyzing the 1999 and 2003 labeling regulations (64 FR 62746 at 62768 and 68 FR 41434 at 41479) and Methods 3 and 4 were based on published methods (Ref. 26). We estimated the change in CHD risk using each of these four methods as applied to two different sets of scenarios for replacement of IP-TFA, as follows.

In general, fats and oils in foods have carbon chains of various lengths, with the carbon atoms in these chains connected by single or double bonds. If the carbon chain contains no double bonds, the fatty acid is called saturated. If the carbon chain contains a single double bond, the fatty acid is called monounsaturated, and if the carbon chain contains two or more double bonds, the fatty acid is called polyunsaturated. Most naturally-occurring dietary unsaturated fatty acids have double bonds in a “cis” configuration, that is, the two hydrogen atoms attached to two carbons are on the same side of the molecule at the double bond. Thus, the major chemical forms of fatty acids in foods are saturated fatty acids (SFAs), cis-monounsaturated fatty acids (cis-MUFAs) and cis-polyunsaturated fatty acids (cis-PUFAs). (By comparison, in a “trans” configuration, the hydrogen atoms attached to the carbon atoms at a double bond are not on the same side of the double bond). (See definitions in 64 FR 62746 at 62748 to 62749 (November 17, 1999)).

One set of scenarios focuses solely on IP-TFA and the estimated change in CHD risk by hypothetically replacing IP-TFA with each of the major chemical forms of macronutrient fatty acids in foods--i.e., SFAs, cis-MUFAs or cis-PUFAs. The other set of scenarios focuses not only on IP-TFA but also on the other fatty acids contained in PHOs. This hypothetical set of scenarios illustrates the estimated change in CHD risk with replacing PHOs in the marketplace

that contain 20 percent, 35 percent, or 45 percent IP-TFA, with other likely replacement fats and oils. Therefore, this scenario accounts for not only the replacement of IP-TFA with macronutrient fatty acids but also the replacement of the overall fatty acid components (or profiles) of the PHOs with the fatty acid components (or profiles) found in the various replacement fats and oils.

In the first set of scenarios, we assumed that the current mean intake of 0.5 percent of total daily calories (energy) from IP-TFA among U.S. adults was replaced by the same percent of energy from three types of macronutrient fatty acids, cis-mono- or polyunsaturated fatty acids and saturated fatty acids) (cis-MUFAs, cis-PUFAs, and SFAs). As measures of risk reduction, we calculated estimated percent changes in CHD risk and estimated reduction in annual total cases of CHD, including CHD-related deaths. We based changes in CHD cases and deaths on a baseline of 915,000 annual new and recurrent fatal and non-fatal cases of CHD in U.S. adults, with a 41 percent fatality rate (Ref. 27).

Results showed an estimated reduction in CHD with replacement of IP-TFA with each of the fatty acids (cis-MUFA, PUFA, or SFA), using each of the four estimation methods. The estimated decrease in CHD ranged from 0.1 percent to 6.0 percent. This corresponded to prevention of 1,180 to 7,510 annual CHD cases, including 490 to 3,120 deaths, in Method 1 (0.1 percent to 0.8 percent decrease in CHD risk based on LDL-C), 9,230 to 15,560 cases, including 3,830 to 6,460 deaths, in Method 2 (1.0 percent to 1.7 percent decrease in CHD risk based on LDL-C and HDL-C), and 18,660 to 54,900 cases, including 7,740 to 22,770 deaths, in Method 3 (2.0 percent to 2.5 percent decrease in CHD risk using a combination of biomarkers) and Method 4 (4.2 percent to 6.0 percent decrease in CHD risk using observed CHD outcomes). Method 4, based on long-term observations of CHD outcomes in prospective studies, produced greater

reduction estimates in risk than did Methods 1 and 2, which were based on short-term changes in blood lipid risk factors in controlled feeding trials. This suggests that there may be additional mechanisms, besides changes in blood lipids, through which trans fat consumption contributes to CHD risk. Thus, the adverse effects from trans fat intake may be greater than predicted solely by changes in blood lipids. The greater estimated reduction in CHD in Method 3, compared with Methods 1 and 2, suggests that the emerging risk factor biomarkers in Method 3 may help to identify additional mechanisms through which trans fat contributes to CHD risk.

In the second set of scenarios, we estimated the reduction in risk by replacing the same 0.5 percent of energy from IP-TFA, along with the other component fatty acids in three different formulations of PHOs, with eight alternative fats and oils (soybean oil, canola oil, cottonseed oil, high oleic sunflower oil, high oleic soybean oil, palm oil, lard, and butter). This approach covers a range of composition of replacement fats and oils, from highly saturated (high in SFAs) to highly unsaturated (high in cis-MUFAs and/or cis-PUFAs), and is based on that reported in 2009 by Mozaffarian and Clarke as part of the World Health Organization (WHO) scientific update on trans fatty acids (Refs. 25 and 26). Among the eight fats and oils, soybean oil and cottonseed oil contain the highest amounts of cis-PUFAs. Canola oil, high oleic acid sunflower oil, and high oleic acid soybean oil have the highest amounts of cis-MUFAs. Butter has the highest amount of SFAs; lard and palm oil are also high in SFAs. We used the same four methods to estimate risk reduction in this analysis. These calculations take into account the fatty acid profiles of the replacement fats and oils and the other fatty acids in the PHOs in addition to IP-TFA.

Overall, the analysis showed that removing 0.5 percent of energy from IP-TFA by replacing an example PHO containing 35 percent IP-TFA with each of eight alternative fats and oils would reduce CHD risk by 0.4 percent to 1.5 percent across the respective replacement fats

and oils using Method 2, 2.3 percent to 3.0 percent using Method 3, and 2.7 percent to 6.4 percent using Method 4. This would correspond to prevention of 3,900 to 58,210 CHD cases including 1,620 to 23,350 CHD deaths per year.

In a few instances, the analysis in the second set of scenarios estimated that there would be increased CHD risk when examples of PHOs were replaced entirely with fats or oils high in saturated fat (Ref. 25) using Method 1. This reflects the saturated fatty acids in alternative fats and oils replacing the cis-unsaturated fatty acids present in the PHO in addition to IP-TFA. Method 1 alone likely underestimates the overall change in risk that would result from replacing PHOs containing IP-TFA because it analyzes only impacts on LDL-C alone and therefore does not account for the demonstrated adverse effects of IP-TFA on HDL-C, or the adverse effects of IP-TFA on other emerging CHD risk factors. Methods 2, 3, and 4 in the second set of scenarios, which consider other known risk factors as well as LDL-C, provides a more thorough estimate of risk reduction than considering only LDL-C in isolation, and leads us to conclude that there would be an expected benefit to public health from PHO replacement even if PHOs are replaced by oils high in saturated fat. Consistent with published analyses, our results show that estimated changes in CHD risk expected to occur with replacement of PHOs depends on the fatty acid profiles of both the PHOs and the replacement fats and oils (Refs. 25, 26, and 28). We also note that research indicates removal of trans fat over the past decade has generally not been accompanied by extensive increases in saturated fat (Ref. 29), suggesting that all IP-TFA currently in the marketplace would not likely be replaced by oils high in saturated fat.

Among the strengths of our quantitative analyses is the use of established cause and effect relationships between IP-TFA intakes and adverse changes in CHD biomarker risk factors, including LDL-C and HDL-C, derived from high quality, controlled feeding trials. Our

assessments also relied on a set of emerging risk factors for CHD, including total cholesterol to HDL-C ratios, Apo-lipoprotein B to Apo-lipoprotein A-I ratios, lipoprotein(a) and C-reactive protein changes obtained from these same feeding trials. In addition, we relied on information from direct observations of CHD outcomes associated with frequent usual intake assessments of trans fatty acids and other macronutrient fatty acids in meta-analyses of four large cohorts with long-term followups. These estimates build on the agency's previous quantitative assessment based on short-term changes in LDL-C and HDL-C alone (68 FR 41434 at 41466 to 41492).

We acknowledge that there are always some uncertainties in assessing risk. The estimates we used were based on 100 percent replacement of IP-TFA by a group of individual types of fatty acids or by individual alternative fats and oils, when actual replacement mixes of fats and oils might vary and individual diets would reflect a combination of replacement fatty acids and replacement fats and oils. We assumed a no threshold, linear relationship between changes in IP-TFA intakes and changes in biomarker risk factors for CHD because current scientific evidence indicates that the relationship between trans fatty acid intake and LDL-C, HDL-C and the total cholesterol to LDL cholesterol ratio is progressive and linear.

Given these uncertainties, our assessments for the change of CHD risk at the current U.S. mean daily intake of 0.5 percent of energy derived from IP-TFA are conservative estimates. The results also suggest that a small shift to lower CHD risk could prevent large numbers of annual cases of CHD and CHD-related deaths. The current U.S. background rates for CHD are already high, with considerable baseline variability due to abnormal serum lipid profiles in large percent of U.S. adults (33.5 percent have elevated LDL-C) and other risk factors for CHD (Ref. 25). More people may be vulnerable to CHD at the current mean intake of IP-TFA from PHOs than the risk reduction estimates as discussed above.

In sum, our quantitative estimates demonstrate that large numbers of CHD events and deaths may be prevented with the elimination of PHOs. We also note that our estimates are in line with published results regarding potential effects of replacing PHOs (Refs. 26 and 28). In replacing PHOs containing IP-TFA, a more significant reduction in CHD risk is estimated by replacement with vegetable oils containing higher amounts of cis-unsaturated fatty acids than with those high in saturated fatty acids, but we expect a risk reduction even if IP-TFA is replaced with fats and oils high in saturated fatty acids, based on our conservative risk estimates using combinations of the four peer-reviewed methods with two different sets of likely scenarios for IP-TFA replacement for each method. Additional details of these results, and results for replacement of example PHOs containing 20 percent IP-TFA and 45 percent IP-TFA, are provided in our review memorandum (Ref. 25).

We have also analyzed the comments we received regarding the scientific basis for our tentative determination in the November 2013 notice. Comments regarding the safety of PHOs that were opposed to our tentative determination were generally related to one of four subject areas: (1) Dose-response relationship of trans fat intake and adverse health effects in human studies and whether there is a threshold below which intake of trans fats is generally recognized as safe; (2) reliance on expert panel reports and recommendations; (3) health benefits and clinical significance of replacements for PHOs; and (4) alternative approaches. Comments regarding the safety of PHOs that were in support of our determination raised concerns about other adverse health effects besides effects on LDL-C, such as adverse effects on other risk factors for CHD (e.g., HDL-C, total-C/HDL-C ratio, LDL-C/HDL-C ratio, and other lipid and non-lipid biomarkers), inflammatory effects, harm to subpopulations, and increased diabetes risk.

1. Dose-Response and Evidence of a Threshold Level

(Comment 26) A number of comments stated that the studies relied upon by FDA were not designed to address the impact of lowering TFA intake below 1% of energy. The comments asserted that although the expert panel reports state that there is no threshold intake level for IP-TFA that would not increase an individual's risk of CHD or adverse effects on risk factors for CHD, a review of the supporting documentation accompanying the reports does not support this statement; rather, the comments noted that panel reports indicate that due to the paucity of evidence in the 0 to 4% energy range, no evidence-based conclusions could be made.

(Response) FDA disagrees; the published research described in our review memorandum (Ref. 18) includes six regression analyses of controlled feeding trials summarizing the dose-response relationship of IP-TFA on blood cholesterol levels, published from 1995 to 2010. In addition, a 2010 meta-analysis included 23 trans fat feeding trials and 28 TFA levels, including a low-dose level of 0.4 percent of energy (or less than the current mean intake) (Ref. 30). Across these regression analyses, the reported effect of TFA on LDL-C, a validated surrogate biomarker that serves as a direct causal link to CHD, was very consistent and the analyses showed a linear dose-response, with an increase in LDL-C of about 0.038 to 0.049 millimoles per liter (mmol/L) for each 1 percent of energy intake from replacement of cis-monounsaturated fat with trans fat (Table 3 in Ref. 18). The regression analyses also showed a consistent linear dose response for HDL-C, with a decrease of about 0.008 to 0.013 mmol/L for each 1 percent of energy from replacement of cis-monounsaturated fat with trans fat (Table 3 in Ref. 18). Therefore, we conclude that the available data show that even at low intake levels (e.g., below 3 percent energy) there is no identifiable threshold, rather the available data support a conclusion that IP-TFA causes a linear increase in blood levels of LDL-C, a validated surrogate biomarker of CHD risk and a linear decrease in blood levels of HDL-C, a major risk biomarker for CHD. If

interested parties are or become aware of information and data supporting establishment of a threshold, such information and data could be submitted to FDA as part of a food additive petition(s) proposing safe conditions of use for PHOs.

(Comment 27) Many comments disagreed with our conclusion that there is a linear relationship between TFA intake and LDL-C at low TFA intake levels. Some comments stated that we did not establish causality between low doses of TFA (less than 1% of caloric energy) and increased CHD risk. Other comments stated that the review of available data shows that low levels of TFA intake (3% of energy or less) have no effect on serum LDL-C and total-C levels. Some comments criticized FDA's reliance on the Ascherio et al. 1999 paper (Ref. 31) and raised issues with this paper and the linear extrapolation used by the researchers. One comment suggested that using a different dose-response model is a more appropriate approach to determine the relationship between PHOs and LDL-C and HDL-C, rather than defaulting to a linear function, due to the quantity and type of data available at low intake levels. One comment stated that, in general, linear regression is an inappropriate tool to determine a safe or unsafe level of a dietary substance and questioned the use of low-dose linear extrapolation in this instance.

(Response) FDA disagrees with these comments. Given that effects of trans fat on LDL-C have been demonstrated at doses as low as 0.4 percent and 2.8 percent of caloric energy (Table 2 in Ref. 18), FDA disagrees that there is no evidence of an adverse effect from trans fat intake below 3percent of energy. In addition, results of regression analyses published from 1995 to 2010, including Ascherio et al. 1999 (Refs. 26, 30, 31, 32, 33, and 34), are very consistent regarding the effect of TFA on serum lipids, thus indicating that the relationship between TFA intake and CHD risk is progressive and linear with no evidence of a threshold at which effects

would not be expected to occur. Furthermore, we are not aware of any published study that supports an abrupt reduction in the adverse effects of TFA across the relatively narrow intake range of 0 percent to 3 percent of energy nor are we aware of any published scientific reports that provide a dose-response model that might reveal a different relationship for TFA intake and CHD risk that is generally accepted by qualified experts. FDA is aware of an unpublished meta-regression analysis, including consideration of the low-intake range (Ref. 35), suggesting that the data on dietary trans fat intake and changes in LDL-C may fit a dose-response curve that is non-linear. However, this analysis is neither published (generally available) nor does it demonstrate a consensus of expert opinion that the use of PHOs at low levels in food is safe as required for general recognition of safety.²

Further, we did not rely solely on the Ascherio et al. 1999 paper regarding the effect of IP-TFA intake on serum LDL-C and other lipid biomarkers. Over time, the number of studies covered by the published regression analyses or meta-analyses increased from 5 studies and 6 TFA levels in 1995 (Ref. 32) through 8 studies and 12 TFA levels in 1999 (Ref. 31) to 23 studies and 28 TFA levels in 2010 (Ref. 30). Across these studies, the reported magnitude of the effect of IP-TFA on LDL-C and HDL-C levels is very consistent. Furthermore, FDA notes that the 2009 National Research Council report, *Science and Decisions: Advancing Risk Assessment* (Ref. 36), describes conceptual models in which low-dose linearity with no threshold can arise. Absent evidence of a threshold intake level for TFA that does not increase an individual's risk of CHD or adverse effects on risk factors for CHD, FDA concludes that a linear low-dose extrapolation is appropriate for assessing the dose-response relationship between TFA intake and

² FDA also reviewed and considered an unpublished report of this analysis and its executive summary, which were submitted to FDA with the request that they be kept confidential. FDA is including these documents in the administrative record for this matter but is not placing them in the public docket because they are confidential.

risk of CHD (as evidenced by effects on LDL-C, a validated surrogate biomarker for CHD, and HDL-C, a risk biomarker (Ref. 18)).

Our conclusion that there is a linear relationship (also known as a proportional effect, or proportionality) between trans fat intake and CHD risk is consistent with the body of evidence from controlled feeding studies on the proportionality of fatty acid intake and blood lipids, beginning with landmark studies in the 1950s and 1960s (Refs. 18, 37, 38, 39, and 40). Meta-analyses in the 1990s and early 2000s showed that the proportionality in the earlier landmark studies extended not only to total cholesterol but to LDL-C, HDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio (Refs. 33, 41, and 42). Authors of a 1992 meta-analysis noted, “a simple linear model in which diets are characterized solely by their contents of saturated, monounsaturated and polyunsaturated fatty acids goes a long way toward predicting group mean changes in serum lipid and lipoprotein levels” (Ref. 42). Results of an early controlled feeding trial of trans fat intake and LDL-C and HDL-C were questioned because of the high trans fat intake (Ref. 43). However, when combined with a subsequent study at a lower dose, preliminary data from these two studies suggested that the effect of trans fat intake on LDL-C and HDL-C is proportional (Ref. 18). Subsequent meta-analyses discussed previously supported the linear proportionality of the data, and the quantitative relationships of dose-response are very consistent across the analyses (Ref. 18). The proportional relationship of trans fat intake and blood lipids has also been repeatedly affirmed by a series of expert panels (Ref. 18). Therefore, we conclude that the totality of the data supports the proportionality of changes in trans fat intake and changes in blood lipids (and therefore, CHD risk) and supports the use of a linear regression model to describe this relationship.

(Comment 28) Some comments objected to the approach of “forcing” the regression line of the dose-response curve through zero (the origin), as done by Ascherio et al. 1999 (Ref. 31) and believed this was not appropriate.

(Response) FDA disagrees. Whether or not to fix the intercept at zero depends on the meaning of the data, the research question to be answered, and the particular study design. (We further discuss the methodology for the meta-analyses in our review memorandum (Ref. 18)). In feeding studies where the total energy intake remains the same for both control and treatment groups, the zero intercept means that, with zero intake of trans fat, there is no effect of trans fat on (that is, no change in) the LDL-C, the LDL-C/HDL-C ratio, or other serum lipid biomarker being studied. This is the one data point that is known to be true by virtue of the study design, and many analyses using this approach have been published in peer-reviewed literature (Refs. 30, 31, 32, 44, and 45). In these analyses, the authors calculated the differences in serum lipid levels between the trans fat diet and the control diet for each controlled feeding trial, with adjustment for differences in intake of the other fatty acids between the two diets, using published dose-response coefficients (Refs. 33 and 42). The serum lipid and trans fat intake differences for each study were included in a linear regression model and expressed with respect to a specific replacement macronutrient (such as cis-monounsaturated fatty acids or carbohydrate). Therefore, we conclude that it is logical and appropriate to fit (not “force”) the regression lines through zero because a zero change in trans fat intake results in zero change in blood lipids attributable to trans fat intake.

(Comment 29) Some comments criticizing our scientific review stated that prospective observational (epidemiological) studies which we relied on were not designed to demonstrate a

cause and effect relationship between a substance and a disease, and are subject to various forms of bias.

(Response) Although observational studies with long-term followup do not prove cause and effect, the results are consistent with and supportive of the conclusions from the controlled feeding trial evidence discussed previously in this section (which does demonstrate cause and effect). The consistency of the evidence from two different study methodologies is strong support for the conclusion that trans fatty acid intake has a progressive and linear effect that increases the risk of CHD. Our review memorandum (Ref. 18) provides a summary of the scientific evidence from the observational studies on the association of TFA intake and actual CHD outcomes in large populations and addresses in detail the study designs and adjustments for confounding variables. There are four major prospective observational studies (Refs. 46, 47, 48, 49, 50, 51, and 52), some with one or more updates during the followup period (e.g., the Nurses' Health Study had followups at 8, 14, and 20 years), that are further discussed in detail in one of our review memoranda (Ref. 18). These are prospective (cohort) studies, which is the strongest study design for observational studies, and the results consistently show that higher trans fat intake is associated with increased CHD risk. In several studies, not only was the association of the highest versus lowest level (category) of trans fat intake with greater CHD risk statistically significant, but also there was a significant test for linear trend, indicating a positive and progressive association of trans fat intake with CHD risk (or CHD deaths) across levels (low, intermediate, or high categories) of intake (Refs. 46, 48, 49, 50, and 51). In addition to the analysis of trans fat intake grouped in several levels or categories, in certain studies, numerical trans fat intake, as a continuous variable, was significantly associated with CHD risk, again

indicating a positive and progressive association of increased trans fat intake with increased CHD risk across the range of observed intake (Refs. 49 and 51).

There are also a number of meta-analyses of the major prospective studies (Refs. 26, 51, 52, 53, 54, and 55). In a 2009 meta-analysis, based on almost 5,000 CHD events in almost 140,000 subjects, each additional 2 percent of energy intake from trans fat increased CHD risk by 23 percent compared with the same energy intake from carbohydrate (Ref. 52). The magnitude of the increase in CHD risk associated with trans fat intake among meta-analyses has remained consistent over time, including the studies with additional updates during the followup periods. Further, the prospective studies measure actual CHD occurrence in large groups of people over long time periods, and describe all CHD risk associated with trans fat intake, regardless of the mechanism of action by which trans fat intake may be associated with CHD (i.e., these studies do not rely on biomarkers or risk factors but instead measure actual occurrence of disease). The magnitude of the observed CHD risk from TFA intake is greater in the prospective observational studies than from the controlled feeding studies.

We also reviewed related observational studies of TFA intake and cardiovascular disease health outcomes that considered all causes of mortality and cardiovascular disease endpoints other than CHD, as well as studies that used blood and tissue levels as biomarkers of TFA intake instead of dietary questionnaires, and retrospective case control studies (Ref. 18). The results from these studies generally showed trans fat intake or biomarkers associated with adverse health outcomes. The consistent findings of adverse health effects of trans fat from these studies with different methodologies strengthen our conclusions based on the evidence from the major prospective observational studies and controlled feeding studies summarized previously.

(Comment 30) Several comments cited a 2011 publication by FDA authors (Ref. 56) as evidence of PHO safety and evidence that a threshold can be determined below which there is general recognition of safety. The comments argued that these authors reviewed data from clinical trials to assess the relationship between trans fat intake and LDL-C and total-C and that their regression analysis showed no association between trans fat consumption and either LDL-C or total-C levels. Also, the comments stated that the authors do not “force” the regression line through zero unlike in the Ascherio et al 1999 paper, relied upon by FDA in the tentative determination.

(Response) FDA disagrees. We note that the authors of this paper stated that their regression analysis of TFA intake and LDL-C “supports the IOM’s conclusion that any intake level of trans fat above 0 percent of energy increased LDL cholesterol concentration.” This paper did not identify a threshold level at which LDL-C began to increase. The analysis in the paper was limited to validated surrogate endpoint biomarkers of CHD, total cholesterol and LDL-C, and did not consider other CHD risk factor biomarkers such as HDL-C, or total-C/HDL-C or LDL-C/HDL-C ratios. The paper focused on methodology for attempting to identify a tolerable upper intake level for trans fat. The appropriateness of fitting the intercept through zero in a regression analysis depends on the meaning of the data, the research question to be answered, and the particular study design, and is discussed further in our response to Comment 28.

In addition to the feeding trial data discussed in the 2011 publication, the authors of the 2011 paper presented data from prospective observational studies showing that, compared with the lowest trans fat intake level, there was a statistically significant increase in CHD risk at some levels of trans fat intake, but not at others. Based on this, they stated that, at least theoretically,

“a threshold level could be identified for trans and saturated fat,” but they were not actually able to identify any specific threshold level. We note that other data from prospective studies that were not discussed in this paper support the conclusion that there is a direct and progressive relationship between TFA intake and CHD risk, and no threshold has been identified. Several studies showed a positive trend for higher CHD risk with higher intake categories of TFA that was statistically significant (Refs. 46, 48, 49, 50, and 51) and certain studies also analyzed numerical TFA intake without using categories (that is, as a continuous variable) and found a significant positive linear association of TFA intake with CHD risk across the range of usual TFA intake levels of participants in the studies (Refs. 49 and 51). These results, not discussed in the paper, are inconsistent with the existence of a threshold. Therefore, we conclude that there is no currently identifiable threshold below which there is general recognition that PHOs may be safely used in human food. However, if there are data and information that demonstrates to a reasonable certainty that no harm will result from a specific use of a PHO in food, that information could be submitted as part of a food additive petition to FDA seeking issuance of a regulation to prescribe conditions under which the additive may be safely used in food.

(Comment 31) Some comments stated that FDA made conclusions that any incremental increase in trans fat intake increases the risk of CHD based on endpoints that are not considered validated surrogate biomarkers for CHD, such as LDL-C/HDL-C ratio in the Ascherio et al. 1999 paper (Ref. 31).

(Response) We used LDL-C, a validated surrogate endpoint biomarker for CHD (Ref. 21), as the primary endpoint for evaluating the adverse effects of IP-TFA intake from PHOs. As discussed previously in this section, validated surrogate endpoint biomarkers are those that have been shown to be valid predictors of disease risk and may therefore be used in place of clinical

measurement of the incidence of disease (Refs. 19 and 20). In addition, we considered the adverse effects of trans fat intake on other risk factor biomarkers, including HDL-C and the LDL-C/HDL-C and total-C/ HDL-C ratios. In fact, these other risk factor biomarkers indicate additional adverse effects of IP-TFA, beyond the primary adverse effect of raising LDL-C. Although these other risk factor biomarkers are not validated surrogate endpoint biomarkers for CHD, they raise significant questions about the safety of PHOs and are therefore relevant to our determination that PHOs are not GRAS. For example, HDL-C levels have been shown to be a useful predictor of CHD risk (Refs. 22 and 57). Because it has not been shown that drug therapy to raise HDL-C decreases CHD in clinical trials, HDL-C is not considered a validated surrogate endpoint for CHD (Ref. 19). We did not primarily rely on the relationship between trans fat intake and adverse effects on HDL-C and CHD risk, we recognize that a relationship is known to exist and therefore considered it in our analysis. We discussed this issue in detail in the July 2003 final rule (68 FR at 41434 at 41448 through 41449).

Recent studies have affirmed HDL-C and total-C/HDL-C ratio as risk factors that predict CHD (Ref. 18). In a large, pooled meta-analysis of prospective observational studies, including 3,020 CHD deaths during 1.5 million person-years of followup, each 1.33 unit decrease in the total-C/HDL-C ratio was associated with a 38 percent decrease in risk of CHD death (Ref. 22). Each 0.33 mmol/L decrease in HDL-C was associated with a 61percent higher risk of CHD death. The authors concluded: "HDL cholesterol added greatly to the predictive ability of total cholesterol." They stated: "Higher HDL cholesterol and lower non-HDL cholesterol levels were approximately independently associated with lower IHD [CHD] mortality, so the ratio of total/HDL cholesterol was substantially more informative about IHD mortality than either, and was more than twice as informative as total cholesterol" (Ref. 22).

(Comment 32) One comment stated that safety evaluation of macronutrients, such as PHOs, is very complex and requires a far more robust assessment of the totality of technical and scientific evidence. The comment criticized FDA for relying on “an isolated physiological endpoint such as serum lipoproteins” as predictive of CHD, and states that this methodology is not appropriate for a GRAS assessment.

(Response) FDA disagrees; the results of feeding trials showing changes in LDL-C, a validated surrogate endpoint biomarker for CHD, and other risk factor biomarkers, are supported by the results of observational studies showing actual CHD disease outcomes (heart attacks and deaths) associated with TFA intake in large populations. The consistency of the evidence from two different study methodologies is strong support for the conclusion that trans fatty acid intake has a progressive and linear effect that increases the risk of CHD. Such health effects are appropriate for FDA to consider when assessing the safety of food ingredients.

2. Expert Panel Reviews and Recommendations

The November 2013 notice discussed expert panel conclusions and recommendations, including the 2002/2005 IOM reports. The conclusions and recommendations of this report have since been affirmed by a series of U.S. and international expert panels. The recent expert panels have continued to recognize the progressive linear relationship between LDL-C (increase) and HDL-C (decrease) and trans fat intake, and have concluded that trans fats are not essential nutrients in the diet and consumption should be kept as low as possible. We have compiled a detailed summary of the expert panel reports in a review memorandum (Ref. 18).

(Comment 33) Some comments stated that FDA should convene an expert panel to specifically address whether evidence exists to indicate the effect of TFA on LDL-C is linear at low intakes (below 3% energy). Other comments stated that there is consensus among qualified

experts that TFA intake should be less than 1% of energy, and cited expert panel reviews as evidence. Similar comments stated that PHOs are safe at current intake levels, and TFA intake is already below levels recommended by nutrition experts.

(Response) We decline to convene another expert panel in light of the substantial evidence available on the adverse effects of consuming trans fat. FDA notes that a 2013 National Institutes of Health, National Heart, Lung, and Blood Institute (NIH/NHLBI) expert panel conducted a systematic evidence review and concluded with moderate confidence that, for every 1percent of energy from TFA replaced by mono- or polyunsaturated fatty acids (MUFA or PUFA), LDL-C decreases by an estimated 1.5 milligrams per deciliter (mg/dL) and 2.0 mg/dL, respectively (Ref. 58). The panel also concluded that replacement of TFA with saturated fatty acids (SFA), MUFA, or PUFA increases HDL-C by an estimated 0.5, 0.4 and 0.5 mg/dL, respectively. This panel's conclusions were not limited to a specific TFA dose range and did not indicate any threshold TFA intake. The conclusions were based on previously published linear regression analyses (Refs. 26 and 33).

We also disagree that, based on generally available information, there is a consensus among qualified experts that trans fats are safe at some level, and we note that recommendations from expert panels either: (1) Do not state a recommended level (Ref. 13); or (2) recommend consideration of further reduction in IP-TFA intake, below current levels (Refs. 59, 60, 61, and 62). Since 2002, many expert panels have considered the adverse effects associated with trans fat consumption. Table 1 provides a list of organizations that have published reports on trans fat and indicates whether they have conducted an evidence review and/or made formal intake recommendations regarding trans fat consumption. The conclusions and recommendations made

by these organizations further demonstrate a lack of consensus regarding the safety of PHOs, as the primary dietary source of IP-TFA.

Table 1.--List of Organizations That Have Published Reports on Trans Fat

Organization	Report Title	Year	Evidence Review and Conclusions	Formal <u>Trans</u> Fat Intake Recommendation
IOM	Dietary Reference Intakes for Energy and Macronutrients (Ref. 7)	2002/2005	X	X
European Food Safety Authority, Scientific Panel on Dietetic Products, Nutrition and Allergies	Opinion on the presence of <u>trans</u> fatty acids in foods and the effect on human health of the consumption of <u>trans</u> fatty acids (Ref.63)	2004	X	
FDA Food Advisory Committee, Nutrition Subcommittee	Subcommittee Meeting, Summary Minutes (Ref. 14)	2004	X	
Dietary Guidelines Advisory Committee (DGAC)	Report of the 2005 DGAC (Ref. 64)	2005	X	
U.S. Dept. of Health and Human Services, U.S. Dept. of Agriculture (DHHS/USDA)	Dietary Guidelines for Americans (Ref. 12)	2005		X
World Health Organization (WHO)	Scientific Update on <u>Trans</u> Fatty Acids (Ref. 60)	2009	X	X
Food and Agriculture Organization, World Health Organization (FAO, WHO)	Background Papers for Expert Consultation on Fats and Fatty Acids in Human Nutrition (Ref.59)	2009	X	
FAO, WHO	Expert Consultation on Fats and Fatty Acids in Human Nutrition (Ref. 61)	2010	X	X
DGAC	Report of the 2010 DGAC (Ref. 65)	2010	X	
DHHS/USDA	Dietary Guidelines for Americans (Ref. 13)	2010		X
NHLBI	Evidence Report on Lifestyles Interventions to Reduce Cardiovascular Risk (Ref. 58)	2013	X	
American College of Cardiology, American Heart Association	Guideline on Lifestyle Management to Reduce Cardiovascular Risk (Ref. 62)	2013/2014		X

3. Safety of Replacements for IP-TFA in PHOs

(Comment 34) Several comments questioned whether further reductions in TFA intake will be clinically significant and subsequently affect public health.

(Response) Since publication of the November 2013 notice, we have quantitatively analyzed the public health significance of removing PHOs from the food supply (Ref. 25), and the results show that removing PHOs from human food would have an expected positive impact on public health. We note that further reductions in IP-TFA intake below current levels may result in small reductions in LDL-C and small improvements in other biomarkers that may not seem clinically significant for an individual; however, when considered across the U.S. population, small reductions in CHD risk would be expected to prevent large numbers of heart attacks and deaths, as illustrated in FDA estimates (Ref. 25). Moreover, the 2013 Guideline on Lifestyle to Reduce Cardiovascular Risk from the American College of Cardiology and the American Heart Association (Ref. 62) strongly recommends that clinicians advise adults who would benefit from LDL-C reduction to reduce their percentage of calories from trans fat (the report notes that the majority of U.S. adults have one or more risk factors involving abnormal lipids, high blood pressure or pre-high blood pressure; 33.5 percent of adults have elevated LDL-C). Therefore, further reduction in IP-TFA intake below current levels is expected to be clinically significant and to prevent a large number of heart attacks and deaths in the United States.

(Comment 35) Some comments stated that the safety implications of replacing TFA with other nutrients (e.g., saturated fat, unsaturated fat, carbohydrates) have yet to be determined.

(Response) We recognize that removing PHOs from the food supply will result in replacing the IP-TFA from PHOs with other macronutrients, most likely other fatty acids, but disagree that the safety implications of these changes have not been considered. The adverse effect of TFA on LDL-C and other blood lipids and non-lipids when replacing other macronutrients (such as carbohydrate, saturated fat and cis-unsaturated fat) was extensively

demonstrated in controlled feeding trials and summarized in regression analyses (Refs. 18, 26, 30, 31, 32, 33, 44, and 45). In prospective observational studies, reduction in CHD risk was also associated with replacement of TFA with other macronutrients (Refs. 18 and 49). These analyses, as well as FDA estimates discussed previously in section IV, demonstrate that replacement of TFA with other macronutrients is expected to result in decreased CHD risk.

We also recognize that replacement of PHOs will result in fatty acids from other fats and oils replacing not only IP-TFA but also the other fatty acids in the PHOs, but disagree that the safety implications of these changes have not been considered. One recent study estimated the change in CHD risk from changes in blood lipids due to replacing soybean oil PHOs with application specific oils (Ref. 28). Results showed that each of the TFA replacement strategies modeled changed the fatty acid intake profile in a manner predicted to decrease CHD risk, with differences in the projected decreased risk due to different replacement oils. Another recent study estimated the effect of the replacement of three example PHOs with seven replacement fats and oils, based on changes in blood lipids and non-lipids and other risk factor biomarkers from controlled feeding trials and on changes in CHD risk from prospective observational studies (Ref. 26). Results showed that replacement of PHOs with other fats and oils would substantially lower CHD risk (Ref. 26). Both studies estimated a greater reduction in CHD risk with replacement of PHOs with vegetable oils containing higher amounts of cis-unsaturated fatty acids than with those high in saturated fat (Refs. 26 and 28). FDA also notes that replacement of PHOs containing IP-TFA with other fats and oils over the past decade has not been accompanied by extensive increases in saturated fat (Ref. 29), which could have diminished the impact of removing trans fat.

The safety implications of replacing IP-TFAs in PHOs with other macronutrients and replacing PHOs containing IP-TFAs with other fats and oils have been addressed in published studies (Refs. 18, 26, 28, 30, 31, 32, 33, 44, 45, and 49) and are also addressed in our quantitative estimate of decrease in CHD risk with replacement of IP-TFA, summarized previously in section IV.B (Ref. 25).

4. Alternative Approaches and Evidence for Safety

In the tentative determination, we requested data to support other possible approaches to address the use of PHOs in food, such as setting a specification for trans fat levels in food (78 FR 67169 at 67174).

(Comment 36) Several comments proposed that we should limit the percentage of trans fat in finished foods or oils, or set a threshold in foods for the maximum grams (g) of trans fat per serving. Some comments suggested various specification levels ranging from 0.2 to 0.5 g trans fat per serving or as a percentage of total fat in foods or oils. Another comment urged FDA to establish a reasonable level for trans fat in food to specifically account for minor uses of PHOs as processing aids.

Some comments urged us to declare that certain uses of PHOs in foods are GRAS, or to issue interim food additive regulations for specific low level uses. Examples of such uses provided by comments included emulsifiers, encapsulates for flavor agents and color additives, pan release agents, anti-caking agents, gum bases, and use in frostings, fillings, and coatings. The use of PHOs in chewing gum was specifically noted in some comments as deserving special consideration due to the claim that there is no meaningful PHO intake from this use. Several comments suggested we issue interim food additive regulations that would allow certain uses of PHOs in food, pending completion of studies evaluating the health effects of low level

consumption of trans fat that reflect current intake levels. Furthermore, one comment advised that if we decide to treat certain low-level uses of PHOs as food additives, then the GRAS status for these uses should not be revoked until a food additive approval is issued.

In contrast, we also received numerous comments opposed to establishing limits of trans fat in foods. Most of these comments noted that scientific evidence has shown that no amount of trans fat in food is safe and therefore, supported our tentative determination. One comment noted that trans fat threshold limits in food would be too difficult to monitor and enforce, and therefore, should not be established.

(Response) Regarding the proposals for alternate approaches suggesting a threshold for trans fat in food or oils or suggesting that FDA declare some uses of PHOs as GRAS, no comments provided evidence that any uses of PHOs meet the GRAS standard, or evidence that would establish a safe threshold exposure level. Further, although the intake from such minor uses may be low, adequate data (e.g., specific conditions of use, use level, trans fat content of the PHOs used) were not provided so that intake from these uses could be estimated. Therefore we are not setting a threshold for trans fat. If industry or other interested individuals believe that safe conditions of use for PHOs can be demonstrated, it or they may submit a food additive petition or food contact notification to FDA for review.

Interim food additive regulations are appropriate only when there is a reasonable certainty that a substance is not harmful. See 21 CFR 180.1(a). As discussed throughout this section, the available scientific evidence raises substantial concerns about the safety of PHOs. Based on the currently available data and information, FDA cannot conclude that there is a reasonable certainty that PHOs are not harmful, nor did any comments provide information that

would allow FDA to establish conditions of safe use at this time. Therefore, an interim food additive regulation would not be appropriate.

(Comment 37) Several comments suggested various changes to our labeling regulations to encourage industry to reformulate products to contain less trans fat and help consumers reduce trans fat intake. In addition, one comment stated that a 0 g trans fat declaration should not be allowed on a label if a PHO is in the ingredient list. Some comments indicated that a statement recommending that consumers limit their intake of trans fat should be added to the Nutrition Facts Panel. A few comments suggested we set a Daily Value for trans fat and consider establishing disclosure or disqualifying levels of trans fat for nutrient content and health claims. Many comments noted that the risk of developing CHD is dependent on many factors, and therefore, the association between intake of macronutrients, such as PHOs, and adverse health outcomes is best addressed through nutrition labeling and consumer education.

(Response) FDA disagrees that labeling is the best approach to address the use of PHOs because FDA has determined that PHOs are not GRAS for any use in human food and therefore are food additives subject to the requirement of premarket approval under section 409 of the FD&C Act. Although we recognize that the requirement to label trans fat content led to significant reduction in trans fat levels in products, further changes to labeling are outside the scope of this determination, which relates to ingredient safety.

(Comment 38) Some comments suggested that we should work with industry to encourage voluntary reductions in PHO use and to foster the development of innovative hydrogenation technologies that produce PHOs containing low levels of trans fat.

(Response) FDA disagrees that a voluntary program is the best way to remove PHOs from the food supply, given our conclusion on the GRAS status of PHOs. FDA has determined

that PHOs are not GRAS for any use in human food. FDA agrees, however, that we should work with the food industry to review new regulatory submissions or data as new technologies and/or ingredients are developed that may serve as alternatives to PHOs, and we will continue to do so.

V. Citizen Petitions

As discussed in the tentative determination (78 FR 67169 at 67173), we received two citizen petitions regarding the safety of PHOs. In 2004, the Center for Science in the Public Interest (CSPI) submitted a citizen petition (“CSPI citizen petition” which can be found under Docket No. FDA-2004-P-0279) requesting that we revoke the GRAS status of PHOs, and consequently declare that PHOs are food additives. The petition also asked us to revoke the safe conditions of use for partially hydrogenated products that are currently considered food additives,³ to prohibit the use of partially hydrogenated vegetable oils that are prior sanctioned, and to initiate a program to encourage manufacturers and restaurants to switch to more healthy oils (CSPI citizen petition at pp. 3 through 5, 29 through 30). The CSPI citizen petition excluded trans fat that occurs naturally in meat from ruminant animals and dairy fats, and that forms during the production of non-hydrogenated oils (Id. at pp. 2 through 3). It also did not include FHOs, which contain negligible amounts of trans fat, and PHOs that may be produced by new technologies that result in negligible amounts of trans fat in the final product (Id. at p. 3). The CSPI citizen petition stated that trans fat promotes CHD by increasing LDL-C and also by lowering HDL-C, and therefore has greater adverse effects on serum lipids (and possibly CHD) than saturated fats (Id., at pp. 15 through 18). The CSPI citizen petition also stated that, beyond

³ The petition from CSPI provided, as an example, partially hydrogenated methyl ester of rosin, which is approved as a food additive for use as a synthetic flavoring substance (32 FR 7946, June 2, 1967; 21 CFR 172.515) and as a masticatory substance in chewing gum base (29 FR 13894, October 8, 1964; 21 CFR 172.615). Partially hydrogenated methyl ester of rosin is not a PHO as discussed in section II; accordingly, this substance is outside the scope of this order.

its adverse effects on serum lipids, trans fat may promote heart disease in additional ways. Based on these findings, CSPI asserted that PHOs can no longer be considered GRAS.

In 2009, Dr. Fred Kummerow submitted a citizen petition (“Kummerow citizen petition,” which can be found at Docket No. FDA-2009-P-0382) requesting that we ban partially hydrogenated fat from the American diet. The Kummerow citizen petition cited studies linking intake of IP-TFA to the prevalence of CHD in the United States. The Kummerow citizen petition also asserted that trans fat may be passed to infants via breast milk and that the daily intake of trans fat related to the health of children has been ignored since children do not exhibit overt heart disease (Id. at p. 6). The Kummerow citizen petition further stated that inflammation in the arteries is believed to be a risk factor in CHD and studies have shown that trans fatty acids elicit an inflammatory response (Id.).

This order constitutes a response, in part, to the citizen petitions. As discussed above in section III.C (response to Comment 10), we plan to amend the regulations regarding LEAR and menhaden PHOs in a future action, and we will consider taking future action regarding related regulations. As discussed in section III.B, we intend to address any claims of prior sanction for specific uses of PHO in a future action.

VI. Environmental Impact

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

FDA received some comments on the tentative determination relating to potential environmental impacts of removing PHOs from the human food supply. We considered these

comments in determining whether extraordinary circumstances existed under 21 CFR 25.21. Our discussion is contained in a review memorandum (Ref. 66).

VII. Economic Analysis

This notice is not a rulemaking. It is a declaratory order under 5 U.S.C. 554(e) to terminate a controversy or remove uncertainty. We have prepared a memorandum updating our previous estimate published in the November 2013 notice, using information available to us as well as information we received during the comment period. We estimated the 20-year costs and benefits of removing PHOs from the U.S. human food supply, an outcome that could result from this order (Ref. 17). We estimated the costs of all significant effects of the removal, including packaged food reformulation and relabeling, increased costs for substitute ingredients, and consumer, restaurant, and bakery recipe changes. We monetized the expected health gains from the removal of PHOs from the food supply using information presented in FDA's safety assessment (Ref. 17) and the peer-reviewed literature, and added this to expected medical expenditure savings to determine the expected benefits of this order.

We estimate the net present value (NPV) (over 20 years; Table 2) of quantified costs of this action to be \$6.2 billion, with a 90 percent confidence interval of \$2.8 billion to \$11 billion. We estimate the net present value of 20 years of benefits to be \$140 billion, with a 90 percent confidence interval of \$11 billion to \$440 billion. Expected NPV of 20 years of net benefits (benefits reduced by quantified costs) are \$130 billion, with a 90 percent confidence interval of \$5 billion to \$430 billion.

Table 2.--Costs and Benefits of PHO Removal, USD Billions

20-Year net present value of	Low Estimate	Mean	High Estimate
Costs*	\$2.8	\$6.2	\$11
Benefits	11	140	440
Net Benefits*	5	130	430

* This does not include some unquantified costs, see the economic estimate memo (Ref. 17) for discussion.

VIII. Compliance Date and Related Comments With FDA Responses

We received numerous comments about the time needed to reformulate products to remove PHOs should FDA make a final determination that PHOs are not GRAS. We also received comments about challenges to reformulation, specific product types that will be difficult to reformulate, and effects on small businesses.

(Comment 39) The comments recommended compliance dates ranging from immediate to over 10 years. Several comments stated that fried foods should have less time (i.e., 6 months) to phase out the use of PHOs. One comment stated that if the use of low levels of PHOs were to remain permissible by virtue of being GRAS or through food additive approval, then the estimated time to reformulate would be 5 years; however, if FDA does not authorize low level uses of PHOs, the timeline would need to be 10 years. In general, the food industry urged FDA to provide sufficient time for all companies to secure a supply of alternatives and transition to new formulations. Some comments stated that FDA should coordinate the compliance date with updates to the Nutrition Facts Panel.

Some comments stated that domestically grown oilseed crops must be planted about 18 months prior to their expected usage in order for the crop to be grown, harvested, stored, crushed, oil extracted, processed, refined, delivered, and used in foods. One comment stated that the oil industry will need a minimum of 3 years to fully commercialize the various oils capable of replacing PHOs in food. A number of comments stated that it could take several additional years to reformulate after the development of the new oils.

Several comments expressed concern about adequate availability of alternative oils, especially palm oil. One comment stated that the food industry would prefer to replace PHOs with domestically produced vegetable oils (e.g., high-oleic soybean oil) rather than palm oil, but

time is needed to commercialize these options. Some comments stated that sudden demand for palm oil would pose challenges for obtaining sustainably-sourced palm oil, as the current market would likely not be able to meet the demand.

Other comments indicated that the time needed for removal of PHOs is dependent on the product category. A number of comments indicated that the baking industry will have difficulty replacing the solid shortenings used in bakery products. Other comments indicated difficulties in the categories of cakes and frostings, fillings for candies, chewing gum, snack bars, and as a component of what the comments termed minor use ingredients, such as for use in coatings, anti-caking agents, encapsulates, emulsifiers, release agents, flavors, and colors.

Several comments indicated that other challenges to PHO removal include the need for new transportation infrastructure (e.g., terminals, rail cars, barges, and storage facilities), packaging changes, and disruption of international trade.

A number of comments noted challenges faced by small businesses, such as access to alternative oils, inability to compete for supply, fewer resources to commit to research and development, and effect of ingredient costs on growth of the business. Some comments noted that small businesses represent a relatively small contribution to overall IP-TFA intake. One comment recommended that we allow small businesses an additional 2 years beyond the rest of industry. Another comment stated that small businesses would need at least 5 years due to their limitations in research and development expertise, inability to command supply of scarce ingredients, and economic pressures of labeling changes. A related comment requested that FDA take into consideration the magnitude of private label products impacted. Other comments stated that small businesses should not be given special consideration or longer times for implementation.

(Response) Based on our experience and on the changes we have already seen in the market, we believe that 3 years is sufficient time for submission and review and, if applicable requirements are met, approval of food additive petitions for uses of PHOs for which industry or other interested individuals believe that safe conditions of use may be prescribed. For this reason, we are establishing a compliance date for this order of June 18, 2018. We recognize that the use of PHOs in the food supply is already declining and expect this to continue even prior to the compliance date. Regarding the use of “low levels” of PHOs, no comments provided a basis upon which we can currently conclude that any use of PHO is GRAS (discussed in section IV). We recognize the challenges faced by small businesses, however, considering our determination that PHOs are not GRAS for any use in human food, we conclude that providing 3 years for submission and review of food additive petitions and/or food contact notifications is reasonable, and will have the additional benefit of allowing small businesses time to address these challenges. We understand the difficulties faced by small businesses due to limited research and development resources and potential challenges to gain timely access to suitable alternatives.

The compliance date will have the additional benefit of minimizing market disruptions by providing industry sufficient time to identify suitable replacement ingredients for PHOs, to exhaust existing product inventories, and to reformulate and modify labeling of affected products. Three years also provides time for the growing, harvesting, and processing of new varieties of edible oilseeds to meet the expected demands for alternative oil products and to address the supply chain issues associated with transition to new oils.

(Comment 40) Several comments stated that how FDA defines PHOs and FHOs will affect reformulation efforts and the time needed to reformulate. These comments suggested it

was unclear from the tentative determination whether FHOs would be subject to this final determination.

(Response) As discussed in section II, we have defined PHOs, the subjects of this order, as fats and oils that have been hydrogenated, but not to complete or near complete saturation, and with an IV greater than 4 as determined by an appropriate method. We have also defined FHOs as those fats and oils that have been hydrogenated to complete or near complete saturation, and with an IV of 4 or less, as determined by an appropriate method. Thus, FHOs are outside the scope of this order and there is no need to allow additional time for reformulation of products containing FHO.

IX. Conclusion and Order

As discussed in this document, for a substance to be GRAS, there must be consensus among qualified experts based on generally available information that the substance is safe under the intended conditions of use. In accordance with the process set forth in FDA's regulations in § 170.38, FDA has determined that there is no longer a consensus that PHOs, the primary source of industrially-produced trans fat, are generally recognized as safe for use in human food, based on current scientific evidence discussed in section IV.B regarding the health risks associated with consumption of trans fat. FDA considers this order a partial response to the citizen petitions from CSPI and Dr. Kummerow.

X. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>.

(FDA has verified the Web site addresses in this reference section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

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