Timothy S. Murbach, ND, DABT
Senior Scientific & Regulatory Consultant
AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000819

Dear Dr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000819. We received the GRAS notice that you submitted on behalf of Wiley Organics, Inc., d/b/a Organic Technologies (Organic Technologies) on October 16, 2018, and filed it on December 20, 2018. Organic Technologies submitted an amendment to the notice on April 7, 2019, that contained additional information on the literature search performed, manufacturing, and analytical methods used.

The subject of the notice is fatty acid ethyl esters (FAEE) from crude oil from Alaska pollock, standardized to contain at least 500 mg/g (50%) or 700 mg/g (70%) palmitoleic acid[1] (hereafter referred to as Pollock FAEE (50% or 70%)) for use as an ingredient in food where standards of identity allow at use levels consistent with current good manufacturing practice. The notice informs us of Organic Technologies' view that these uses of Pollock FAEE (50% or 70%) are GRAS through scientific procedures. The notifier states that the ingredients are not intended for use in infant formula or in products that are subject to regulation by the United States Department of Agriculture.

Our use of the term, "Pollock FAEE (50% or 70%)" in this letter is not our recommendation of that term as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for "Pollock FAEE (50% or 70%)."

Organic Technologies describes the method of manufacture for Pollock FAEE (50% or 70%). Organic Technologies states that crude oil from Alaska pollock is first distilled to remove free fatty acids and impurities, and the fatty acids in the form of triglycerides are

[1] We note that palmitoleic acid is identified as C16:1; CAS Registry No. 56219-10-4; CAS Index name: 9-hexadecenoic acid, ethyl ester, (9Z)-.

cleaved and then reacted with ethanol to form ethyl esters. The resulting FAEE mixture is further purified, and the fatty acid profile is modified using distillation, winterization, and filtration. Organic Technologies explains that the percentages of palmitoleic, palmitic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are controlled using crystallization and distillation techniques.

Organic Technologies provides specifications for Pollock FAEE. Organic Technologies provides batch analyses from five non-consecutive lots of Pollock FAEE (50% or 70%) to demonstrate that the two products can be manufactured to conform with the specifications. A typical fatty acid profile[2] provided by Organic Technologies indicates that the products contain 10-20% palmitic acid. The notifier also notes that EPA and DHA should be present at no more than 2 mg/g (0.2%).

Organic Technologies estimates the dietary exposure to the two products using consumption data from the National Health and Nutrition Examination Surveys (NHANES) (2013-2014). The notifier analyzed the dietary fat consumption data from NHANES using the Creme Food Safety software. Assuming that 100% of fat consumed by the US population (ages 2+) is replaced by Pollock FAEE (50% or 70%), Organic Technologies calculated that the total 90$^{th}$ percentile lifetime dietary exposure to the products to be 115.7 g/day. However, taking into account the organoleptic properties of the products, cost, and market share limitations, and the fact that most foods contain an endogenous amount of fat,[3] Organic Technologies refined their estimate and calculated exposure based on replacement of only 10% of dietary fat. This results in an exposure of Pollock FAEE (50% or 70%) of 11.57 g/day at the 90$^{th}$ percentile. Organic Technologies estimated exposure of palmitoleic acid ethyl ester (EE) from Pollock FAEE 50% and Pollock FAEE 70% to be 5.85 g/day and 8.33 g/day, respectively.

Organic Technologies discusses the absorption, distribution, metabolism, and excretion of dietary FAEEs, including palmitoleic acid EE, the principal component of Pollock FAEE. Organic Technologies notes that the outcome of the digestion of FAEEs is the release of free fatty acids and ethanol. Organic Technologies states that the released ethanol during digestion of FAEEs is not significant and is at levels expected from consumption of common foods such as vanilla ice cream and orange juice. Organic Technologies provides evidence from human studies that dietary intake of palmitoleic acid EE leads to an increase in plasma palmitoleic acid, but that the endogenous *de novo* synthesis of the monounsaturated palmitoleic acid from saturated fatty acids (e.g., palmitic acid) is a minor source of plasma palmitoleic acid.

Organic Technologies states that exposure to palmitoleic acid EE from the consumption of common ingredients is limited in comparison to the availability of other dietary FAEEs because few foods regularly eaten contain significant levels of palmitoleic acid. Organic Technologies notes that some dietary sources containing this fatty acid are certain fish oils and the macadamia nut and its oil, which range from 4.8% to 17%

[2] In the amendment received on April 7, 2019, Organic Technologies explains that the values in the profile were generated from a single batch analysis each of Pollock FAEE 50% and 70% using a method based on AOCS Ce 1b-89.

[3] The products will be used as an ingredient, not as a fat replacement.

palmitoleic acid content. In contrast, the two Pollock FAEE products contain 50% and 70% palmitoleic acid EE, along with lower levels of a wide range of other edible FAEEs. Because of the additional dietary exposure to palmitoleic acid from consumption of food products that have had fats or oils replaced with the Pollock FAEE (50% or 70%) products, Organic Technologies focuses on the evaluation of the safety of oral exposure to palmitoleic acid.[4] In its assessment, Organic Technologies reviewed available published studies that administered oils, seeds, or pulp test substances that contained varying percentages of palmitoleic acid, along with some mixtures of other fatty acids such as EPA, linoleic acid, palmitic acid, and/or oleic acid.

Organic Technologies discusses the results of published toxicology studies that tested oils containing palmitoleic acid EE in bacterial reverse mutation, *in vitro* mammalian chromosomal aberration, and *in vivo* mammalian micronucleus assays, as well as an acute oral toxicity study in rats. Organic Technologies also describes several published studies in humans who were orally exposed to palmitoleic acid EE along with other FAEEs via either test oil, pulp, seeds, or ingredients for 1 to 4 months. Based on the findings of these studies, Organic Technologies concludes that no toxicologically and clinically relevant adverse effects are associated with dietary exposure to palmitoleic acid EE. Organic Technologies reports it conducted several literature searches at different times spanning from July 2016 through September 2018.

Based on the totality of data and information described above, Organic Technologies concludes that Pollock FAEE (50% or 70%) is GRAS under the intended conditions of use.

## Potential Labeling Issues

Under section 403(a) of the Federal Food Drug and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient levelin a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). The notice raises a potential issue under these labeling provisions. In the notice, Organic Technologies cites studies that describe Pollock FAEE (50% or 70%) as having certain health benefits. If products containing Pollock FAEE (50% or 70%) bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of ONFL. OFAS did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

## Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that

[4] GRN 000494 describes the use of FAEE derived from anchovy or menhaden oil and standardized to approximately 50% palmitoleic acid. FDA evaluated this notice and responded in a letter December 16, 2014, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

contains a “major food allergen” declare the allergen’s presence (section 403(w)). The FD&C Act defines a “major food allergen” as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. Pollock FAEE (50% or 70%) derived from Alaska pollock may require labeling under the FD&C Act because it may contain protein derived from fish. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL.

**Section 301(ll) of the FD&C Act**

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of Organic Technologies’ notice concluding that Pollock FAEE (50% or 70%) is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing Pollock FAEE (50% or 70%). Accordingly, our response should not be construed to be a statement that foods containing Pollock FAEE (50% or 70%), if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

**Conclusions**

Based on the information that Organic Technologies provided, as well as other information available to FDA, we have no questions at this time regarding Organic Technologies’ conclusion that Pollock FAEE (50% or 70%) is GRAS under its intended conditions of use. This letter is not an affirmation that Pollock FAEE (50% or 70%) is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000819 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.09.03 13:55:07 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition