



Kathleen M. Sanzo  
Morgan, Lewis and Bockius LLP  
1111 Pennsylvania Avenue NW  
Washington, DC 20004

Re: GRAS Notice No. GRN 000914

Dear Ms. Sanzo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000914. We received the notice that you submitted on behalf of Kao Corporation (Kao) on February 26, 2020 and filed it on May 4, 2020. Kao submitted amendments to the notice on September 29, 2020 and February 19, 2021, that provided clarifications and additional information on the intended use, manufacturing process, specifications, analytical methods, batch data, stability studies, dietary exposure, and safety of the subject of the notice.

The subject of the notice is *alpha*-linolenic acid diacylglycerol (ALA DAG) oil for use as a partial replacement for edible salad oils and other dressings sprayed onto salads, vegetables and other finished foods at a level of 2.5 g/serving.<sup>1</sup> The notice informs us of Kao's view that this use of ALA DAG oil is GRAS through scientific procedures.

Our use of the terms, "*alpha*-linolenic acid diacylglycerol" or "ALA DAG," 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 did not consult with ONFL regarding the appropriate common or usual name for "ALA DAG."

Kao provides information on the identity and composition of ALA DAG oil. Kao states that ALA DAG oil is primarily composed of diacylglycerol, with smaller amounts of monoacylglycerol, triacylglycerol, and free fatty acids. Kao also notes that ALA DAG oil was analyzed for the presence of phytosterols from the starting flaxseed oil. Kao states that ALA DAG oil contains small quantities of sterols that are consistent with the levels

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<sup>1</sup> Kao states that ALA DAG oil is not intended for use in infant formula or products under the jurisdiction of USDA.

of phytosterols in GRN 000256<sup>2</sup> and with those in commercially available cold-pressed flaxseed oil. Kao provides the fatty acid composition of the diacylglycerol component and states that ALA is the most abundant fatty acid, with lower levels of oleic, linoleic, stearic, and palmitic acids present.

Kao describes the method of manufacture for ALA DAG oil starting with the enzymatic hydrolysis of flaxseed oil at mild temperatures under nitrogen to produce fatty acids. The fatty acids are then crystallized by polyglycerol fatty acid esters and fractionated at cool temperatures under nitrogen. The solid portion is removed and the solution containing the fatty acids and glycerin is passed through an ion exchange resin to enzymatically esterify the fatty acids. The solution is then distilled to yield crude ALA DAG oil. Next, the crude ALA DAG oil is subjected to a series of washing steps with citric acid and water under nitrogen in a centrifuge, and then steam deodorized and bleached with activated clay (bentonite). Finally, the solution is again deodorized to produce the ALA DAG oil. Kao states that ALA DAG oil is manufactured in accordance with current good manufacturing practices and that all raw materials, processing aids, and additives used in the production of the ALA DAG oil are food-grade or equivalent and are used in accordance with applicable FDA regulations or have previously been concluded to be GRAS.

Kao provides specifications for ALA DAG oil as follows: ALA DAG ( $\geq 36\%$  by weight); peroxide value ( $\leq 5$  meq/kg); acid value ( $\leq 2$  mg KOH/g); moisture ( $\leq 0.1\%$  by weight); lead ( $\leq 0.5$  mg/kg); arsenic ( $\leq 0.5$  mg/kg); cadmium ( $\leq 0.2$  mg/kg); and mercury ( $\leq 0.1$  mg/kg). Kao provides analyses from three nonconsecutive lots of ALA DAG oil to demonstrate conformance with the stated specifications. Kao provides results of a one-month stability study and indicates that ALA DAG oil is stable for one month at 30 °C under nitrogen.

Kao states that ALA DAG is naturally occurring at low levels in flaxseed oil and rapeseed (canola) oil and therefore there is background exposure to ALA DAG for the U.S. population through consumption of these oils. Kao estimates the background dietary exposure to flaxseed, flaxseed oil, and rapeseed (canola) oil using the U.S. Environmental Protection Agency Food Commodity Intake Database. Using the 2-day average consumption levels, Kao estimates the background per capita dietary exposure to flaxseed and flaxseed oil to be 27.7 g/d or 0.4 g/kg body weight (bw)/d. Kao estimates the background per capita dietary exposure to rapeseed (canola) oil to be 60.3 g/d or 1.6 g/kg bw/d. Kao then determines the ALA DAG content of flaxseed oil and rapeseed (canola) oil and uses the mean levels to estimate the exposure to ALA DAG from the consumption of flaxseed oil and rapeseed (canola) oil. Based on the levels of ALA DAG in these two oils, Kao estimates the background dietary exposure of ALA DAG to be 0.49 g/d.

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<sup>2</sup> The subject of GRN 000256 was high linolenic acid flaxseed oil. We evaluated this notice and responded in a letter dated January 16, 2009, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Kao states that ALA DAG oil will be used at a level of 2.5 g per serving, and that the ALA DAG oil will contain at least 36% ALA DAG. Therefore, the exposure to ALA DAG from the intended use of ALA DAG oil is 0.9 g/d.<sup>3</sup> Kao states that the overall daily dietary consumption of ALA DAG from the background exposure to ALA DAG and the intended uses of ALA DAG oil would be 1.39 g/d.

Kao states that the safety of ALA DAG oil is based on available product-specific published and unpublished studies. Kao provides a general discussion regarding the absorption, distribution and metabolism of diacylglycerol and triacylglycerol. Kao states the overall metabolic pathway of ALA DAG oil is expected to be similar to that of diacylglycerol oil as reported in the published literature and summarized by Kao. Kao discusses the published toxicological studies on ALA DAG oil in rats. In a 90-day dietary study, no toxicologically relevant effects were observed at 5.5% ALA DAG oil in the diet (equal to 2,916-3,326 mg/kg bw/d), the highest concentration tested. In a 24-week oral carcinogenesis study intended to investigate the tumorigenesis potential of ALA DAG oil on tongue and digestive tract tissues, ALA DAG oil did not promote tumor development in the digestive system at concentrations up to 55,000 ppm in the diet (equal to 2,397 mg/kg bw/d). Additionally, Kao discusses a published prenatal developmental toxicity study which showed no toxicologically relevant effects at doses up to 5.0 mL/kg bw/d (equal to 4,715 mg/kg bw/d). Kao summarizes published genotoxicity tests and states that ALA DAG oil is not mutagenic or genotoxic. Kao also discusses clinical studies demonstrating that consumption of ALA DAG oil is well-tolerated and not expected to have a deleterious effect on the bioavailability of fat-soluble vitamins. Kao reports on epidemiological studies to support the safe use of ALA DAG oil and states that the intended uses of ALA DAG oil would not be expected to pose a safety concern with respect to prostate cancer and age-related macular degeneration.

Kao includes the statement of a panel of individuals (Kao's GRAS panel). Based on its review, Kao's GRAS panel concluded that ALA DAG oil is safe under the conditions of its intended use.

Based on the totality of the data and information, Kao concludes that ALA DAG oil is GRAS for its intended use.

### **Standards of Identity**

In the notice, Kao states its intention to use ALA DAG oil in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

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<sup>3</sup> 2.5 g/d x 36% = 0.9 g/d. Kao states that there is no maximum specification for ALA DAG in the oil, but that they routinely standardize the product to contain 39% ALA DAG. We note that this would result in an exposure to ALA DAG of 1.0 g/d from the intended use and a cumulative exposure to ALA DAG of 1.49 g/d.

## **Potential Labeling Issues**

Under section 403(a) of the 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 level in 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). If products containing ALA DAG oil 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. The Office of Food Additive Safety 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.

## **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 Kao's notice concluding that ALA DAG 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 ALA DAG. Accordingly, our response should not be construed to be a statement that foods containing ALA DAG, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).


## **Conclusions**

Based on the information that Kao provided, as well as other information available to FDA, we have no questions at this time regarding Kao's conclusion that ALA DAG is GRAS under its intended conditions of use. This letter is not an affirmation that ALA DAG 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 000914 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.  
Carlson -S

 Digitally signed by Susan J.  
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Susan Carlson, Ph.D.  
Director  
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