



Susan Cho, Ph.D.  
NutraSource, Inc.  
6309 Morning Dew Court  
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000730

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000730. We received the GRAS notice that you submitted on behalf of Linyi Youkang Biology Co., Ltd. (Linyi Youkang) on September 14, 2017 and filed it on October 26, 2017. Linyi Youkang submitted amendments to the notice on January 4, 2018 and January 26, 2018 that contained additional safety and identity information, and on March 7, 2018 that contained a revised Part 1. Signed Statements and a Certification.

The subject of the notice is arachidonic acid-rich oil from *Mortierella alpina* strain LU 166 (ARA-rich oil) for use as an ingredient in milk- and soy-based infant formulas. The maximum level for non-exempt term infant formula is 0.75% ARA and for exempt pre-term infant formula is 0.40% ARA by weight of total fatty acids in combination with docosahexaenoic acid (DHA) at a ratio ranging from 1:1 to 2:1. The notice informs us of Linyi Youkang's view that these uses of ARA-rich oil are GRAS through scientific procedures.

Our use of the term, "ARA-rich oil" 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 Code of Federal Regulations (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 "ARA-rich oil."

Linyi Youkang describes ARA-rich oil as a yellow oil with  $\geq 40\%$  of the fatty acids as ARA. The ARA-rich oil is produced by the fungus *M. alpina*. ARA is a carboxylic acid with a carbon chain length of 20 and four cis-double bonds (chemical name: all cis-5,8,11,14-eicosatetraenoic acid). Its molecular formula is  $C_{20}H_{32}O_2$  with CAS No. 506-32-1.

Linyi Youkang describes the manufacture of ARA-rich oil from production strain *M.*

U.S. Food and Drug Administration  
Center for Food Safety & Applied Nutrition  
5001 Campus Drive  
College Park, MD 20740  
[www.fda.gov](http://www.fda.gov)

*alpina* LU 166.<sup>1</sup> Cultures are fermented in nutrient-rich broth containing glucose and yeast powder under aerobic conditions. The resulting ARA-rich biomass is filtered, dried, and extracted with hexane to yield crude ARA-rich oil. The crude oil is further refined by water degumming, acid degumming, alkali adjustment with sodium hydroxide, decolorization, and deodorization with steam to remove any remaining volatile components. The final step is the addition of vitamin E, which increases the oxidative stability of the oil, followed by packaging under vacuum. Linyi Youkang states that ARA-rich oil is produced in accordance with current good manufacturing practices. All growth media, raw materials, and processing aids used in the fermentation and manufacturing processes are food-grade.

Linyi Youkang provides specifications for ARA-rich oil ( $\geq 40\%$  ARA), peroxide value ( $< 2.5$  milliequivalents (meq)/kg oil), and limits on residual hexane ( $\leq 1.0$  mg/kg), heavy metals ( $< 0.1$  mg/kg), and aerobic microbes ( $< 10$  cfu/mL). Linyi Youkang provides the results of three non-consecutive batch analyses of the oil to demonstrate that the ingredient can be manufactured to meet these specifications.

Linyi Youkang estimates the dietary exposure to ARA from ARA-rich oil, which they state will be the same as in GRN 000326.<sup>2</sup> The mean dietary exposures to ARA are 27 mg/kg bodyweight (bw)/day (d) and 42 mg/kg bw/d for pre-term and term infants, respectively. These estimates are based on the following assumptions: (1) pre-term infants consume 120 kilocalories (kcal)/kg bw/d and term infants consume 100 kcal/kg bw/d, (2) fat comprises  $\sim 50\%$  of the available energy in human milk or infant formula, and (3) pre-term infants consume  $\sim 6.7$  g fat/kg bw/d and term infants consume  $\sim 5.6$  g fat/kg bw/d.

Linyi Youkang discusses the safety of ARA-rich oil and incorporates safety and metabolism studies into the notice from GRNs 000041, 000080, 000094, and 000326.<sup>2</sup> Linyi Youkang states that the ARA-rich oil that is the subject of GRN 000730 is equivalent to ARA-rich oils described in these notices.

Linyi Youkang summarizes published information on the metabolic fate of ARA-rich oil. Linyi Youkang also describes publicly available safety information described in GRN 000326, including mutagenicity and genotoxicity studies, acute and/or subchronic studies in rats and piglets, and a developmental and reproductive toxicity study in rats. As corroborative information, Linyi Youkang describes their unpublished rat acute toxicity study using the ARA-rich oil that is the subject of GRN 000730, which showed no adverse effects. Based on all the toxicology data evaluated, Linyi Youkang concludes that there is no evidence of toxicity up to 5,000 mg/kg bw/d, the highest dose tested in rats. Linyi Youkang also summarizes published human studies with pre-term and term infants discussed in GRN 000326, as well as those published after its submission. Linyi Youkang discusses endpoints related to safety and physiology in these human studies

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<sup>1</sup> Linyi Youkang states that the production strain *M. alpina* LU 166 is not pathogenic or toxigenic.

<sup>2</sup> ARA-rich oil in combination with DHA-rich oil was the subject of GRNs 000041, 000080, 000094, and 000326. We evaluated these notices and responded in letters dated May 17, 2001; December 11, 2001; April 18, 2006; and October 24, 2010, respectively, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

that support the safety of ARA-rich oil. Finally, Linyi Youkang discusses other published information identified by literature searches through July 2017 and concludes that new information does not contradict the safety of ARA-rich oil.

Based on the totality of the data and information described above, Linyi Youkang concludes that the intended use of ARA-rich oil is generally recognized as safe.

### **Potential Labeling Issues**

Under section 403(a) of the Federal Food, Drug, and Cosmetic (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). The notice raises a potential issue under these labeling provisions. Linyi Youkang cites studies that describe ARA-rich oil as having certain health benefits. If products containing ARA-rich 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. 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.

### **Intended Use in Infant Formula**

Under section 412 of the FD&C Act, a manufacturer of a new infant formula must make a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Linyi Youkang's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing ARA-rich oil to make the submission required by section 412. Infant formulas are the purview of ONFL.

### **Section 301(II) of the FD&C Act**

Section 301(II) 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(II)(1)-(4) applies. In our evaluation of Linyi Youkang's notice concluding that ARA-rich oil is GRAS under its intended conditions of use, we did not consider whether section 301(II) or any of its exemptions apply to foods containing ARA-rich oil. Accordingly, our response should not be construed to be a statement that foods containing ARA-rich oil, if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

### **Conclusions**

Based on the information that Linyi Youkang provided, as well as other information

available to FDA, we have no questions at this time regarding Linyi Youkang's conclusion that ARA-rich oil is GRAS under its intended conditions of use. This letter is not an affirmation that ARA-rich oil 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 000730 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Michael A.  
Adams -S

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A. Adams -S  
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Dennis M. Keefe, Ph.D.  
Director  
Office of Food Additive Safety  
Center for Food Safety  
and Applied Nutrition