Claire Kruger, Ph.D., DABT, CFS
Spherix Consulting Group, Inc.
751 Rockville Pike, Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001115

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001115. We received the notice you submitted on behalf of Hubei Fuxing Biotechnology Co., Ltd. (Hubei Fuxing) on September 27, 2022, and filed it on March 23, 2023. Hubei Fuxing submitted an amendment to the notice on August 3, 2023, that clarified the intended use, manufacturing, specifications, and aspects of the safety narrative.

The subject of the notice is fungal oil (≥40% arachidonic acid (ARA)) from *Mortierella alpina* strain AF (*M. alpina* oil) for use as an ingredient in cow milk- and soy-based, non-exempt infant formula for term infants at levels providing up to 0.75% of fat as ARA and in exempt infant formula for pre-term infants at levels providing up to 0.4% of fat as ARA. Hubei Fuxing states that *M. alpina* oil will be used in combination with a safe and suitable source of docosahexaenoic acid (DHA) at a ratio ranging from 1:1 to 2:1 ARA:DHA. The notice informs us of Hubei Fuxing's view that these uses of *M. alpina* oil are GRAS through scientific procedures.

Our use of the term "*M. alpina* 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 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 "*M. alpina* oil."

Hubei Fuxing describes *M. alpina* oil as a pale to dark yellow oil with ≥40% by weight of total fatty acids (TFA) as ARA. ARA is an omega-6 fatty acid with a carbon chain length of 20 and four cis-double bonds (20:4 n-6). The chemical name is (all cis)-5,8,11,14-eicosatetraenoic acid. The predominant fatty acids and their typical ranges (expressed as %TFA) in *M. alpina* oil include palmitic acid (9.6-9.9%), stearic acid (6.3-6.6%), oleic

acid (5.3-5.7%), linoleic acid (7.1-8.5%), gamma-linolenic acid (2.7-2.9%), dihomo-gamma-linolenic acid (5.0-5.7%), behenic acid (2.9-3.0%), lignoceric acid (9.1-9.7%), and ARA (44.8-46.0%).[1] Total sterols are present at ~1% (by weight) of the *M. alpina* oil.

Hubei Fuxing describes the manufacture of *M. alpina* oil produced by fermentation using the production strain *M. alpina* AF, deposited at the Type Culture Collection Committee of the Chinese Academy of Sciences (CGMCC) under deposit number CGMCC 0903. *M. alpina* is fermented under aerobic conditions in the absence of light in a closed system and is monitored for microbial contamination and controlled to ensure consistent pH, aeration rate, and temperature. After fermentation is complete, the biomass is filtered from the medium and washed three times with sterilized water, dried, and extracted with butane to yield crude *M. alpina* oil. After evaporation of the solvent, the crude oil is degummed, neutralized with alkali solution, and washed with water. The oil is bleached using activated carbon and activated clay (kaolin) and is then filtered and deodorized using standard procedures. Residual volatile components are removed by deodorization. The refined oil is then filtered, and antioxidants are added. Hubei Fuxing states that *M. alpina* oil is produced in accordance with current good manufacturing practices and that raw materials and processing aids used in the manufacturing process are safe and suitable for their intended use, are used in accordance with applicable U.S. regulations, and are GRAS for their intended use, or are the subject of an effective food contact notification.

Hubei Fuxing provides specifications for *M. alpina* oil that include the minimum content of ARA (≥40% weight basis) and limits for acid value (≤0.5 mg potassium hydroxide/g), free fatty acids (≤0.2%), peroxide value (≤2.0 milliequivalents/kg), *p*-anisidine value (≤10), unsaponifiable matter (≤3.0%), residual solvent (butane ≤1 mg/kg), lead (<0.1 mg/kg), and microorganisms, including *Salmonella* serovars (negative in 25 g) and *Cronobacter sakazakii* (negative in 100 mL). Quality specifications are consistent with those stated in the 13th Edition of the Food Chemicals Codex (FCC, 2023).[1] Hubei Fuxing provides the results of three non-consecutive batch analyses to demonstrate that *M. alpina* oil can be manufactured to meet these specifications. Based on stability studies performed by Hubei Fuxing, *M. alpina* oil is stable under ambient conditions (25 °C, 75% humidity) for 12 months.

Hubei Fuxing estimates the dietary exposure to ARA from the intended uses of *M. alpina* oil based on the following assumptions: (1) pre-term infants consume 120 kilocalories (kcal)/kg body weight (bw)/day (d), and term infants consume 100 kcal/kg bw/d, (2) fat comprises 50% of the available energy in human milk or infant formula, and (3) one g of fat is equivalent to 9 kcal. Hubei Fuxing estimates that pre-term infants consume 6.7 g fat/kg bw/d and term infants consume 5.6 g fat/kg bw/d, with estimated dietary exposures to ARA of 27 mg/kg bw/d for pre-term infants and 42 mg/kg bw/d for term infants. Hubei Fuxing notes that its use levels and estimates of dietary exposure to ARA are consistent with those reported in previous GRNs (GRN 000326, GRN

[1] In comparison to the FCC (13th Ed., 2023) monograph for "ARA from Fungal (*Mortierella alpina*) Oil," *M. alpina* oil contains a similar profile of major fatty acids and low levels of arachidic acid (<1%).

000963).[2]

Hubei Fuxing discusses data and information supporting the safety of *M. alpina* oil and states that an updated literature search conducted through May 2022 did not identify any new toxicology or genotoxicity studies. Based on a comparison between the manufacturing processes and finished product specifications, Hubei Fuxing states that the article of commerce is compositionally similar to *M. alpina* oils previously concluded to be GRAS for their intended uses. Therefore, Hubei Fuxing concludes that the safety of the article of commerce is equivalent to the safety of other *M. alpina* oils and incorporates into the notice published and unpublished safety and metabolism studies from GRNs 000041, 000080, 000094, 000326, 000730, and 000963.[2] Specifically, Hubei Fuxing discusses acute, subchronic, and developmental/reproductive toxicity studies in rats and mice, tolerance studies in neonatal piglets, and genotoxicity studies, which demonstrate a lack of adverse effects.

To further support the safety of the subject of the notice, Hubei Fuxing discusses the safety of fatty acids and sterols present in *M. alpina* oils. Hubei Fuxing notes that the fatty acid profile for the subject of the notice is equivalent to the fatty acid profiles described for *M. alpina* oils in GRNs 000094, 000326, and 000730, noting that any differences in specific fatty acids are not expected to affect the safety of the ingredient. Additionally, Hubei Fuxing states that the estimated dietary exposure to sterols from infant formulas containing the article of commerce are consistent with compositional analyses and dietary exposure estimates to sterols from *M. alpina* oils in GRNs 000041, 000080, 000094, 000326, 000730, and 000963.

Hubei Fuxing also discusses a recent clinical study and incorporates into the notice published clinical studies in infants from GRNs 000326, 000730, and 000963. Hubei Fuxing concludes that the use of *M. alpina* oil is safe and well-tolerated in term and pre-term infants.

Based on the totality of the data and information, Hubei Fuxing concludes that *M. alpina* oil is GRAS for its intended use.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, & 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). If products containing *M. alpina* 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.

[2]ARA-containing *M. alpina* oil, in combination with a safe and suitable source of DHA, was the subject of GRNs 000041, 000080, 000094, 000326, 000730, and 000963. We evaluated these notices and responded in letters dated May 17, 2001, December 11, 2001, April 18, 2006, February 16, 2011, March 30, 2018, and October 19, 2021, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Hubei Fuxing notes that *M. alpina* oil has color. As such, the use of *M. alpina* oil in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring. Our response to GRN 001115 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

Intended Use in Infant Formulas

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 Hubei Fuxing's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *M. alpina* oil to make the submission required by section 412. Infant formulas are the purview of 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 Hubei Fuxing's notice concluding that *M. alpina* oil 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 *M. alpina* oil. Accordingly, our response should not be construed to be a statement that foods containing *M. alpina* oil, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Hubei Fuxing provided, as well as other information available to FDA, we have no questions at this time regarding Hubei Fuxing's conclusion that *M. alpina* oil is GRAS under its intended conditions of use. This letter is not an

affirmation that *M. alpina* 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 001115 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.09.18 17:03:06 -04'00'

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Director
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