Donald F. Schmitt, MPH
ToxStrategies, Inc.
931 W. 75th St., Suite 137, PMB 255
Naperville, IL 60565

Re: GRAS Notice No. GRN 000963

Dear Mr. Schmitt:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000963. We received the notice that you submitted on behalf of BASF Corporation (BASF) on August 6, 2020, and filed it on December 21, 2020. BASF submitted amendments to the notice on January 7, 2021, January 15, 2021, March 3, 2021, May 28, 2021, August 5, 2021, and September 17, 2021, that amended the intended use and specifications, clarified estimated dietary exposure and production strain deposit information, and provided additional details of several safety studies.

The subject of the notice is oil from *Mortierella alpina* containing ≥40% arachidonic acid (*M. alpina* oil) for use as an ingredient in cow milk-and soy-based non-exempt infant formulas for term infants at levels providing up to 0.75% of fat as arachidonic acid (ARA) and in exempt infant formula for pre-term infants at levels providing up to 0.4% of fat as ARA. The *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 BASF's view that these uses of *M. alpina* oil are GRAS through scientific procedures.

Our use of the term, "oil from *Mortierella alpina* containing ≥40% arachidonic acid (*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 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 (CFSAN). The Office of Food Additive Safety (OFAS) did not consult with ONFL regarding the appropriate common or usual name for, "oil from *Mortierella alpina* containing ≥40% arachidonic acid (*M. alpina* oil)."

BASF describes *M. alpina* oil as a light yellow to orange oil with ≥40% by weight of total fatty acids 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, and the molecular formula is $C_{20}H_{32}O_2$. Other major fatty acids present in *M. alpina* oil include, with approximate levels, palmitic acid (6-10%), stearic

acid (8-10%), oleic acid (16-22%), and linoleic acid (5-6%).[1] Total sterols are present at 1-2% in *M. alpina* oil.

BASF describes the manufacture of *M. alpina* oil produced by fermentation using one of two production strains of *M. alpina*: XM027 or CNCM I-4642.[2] BASF notes that the fermentation process is similar to those described in previous GRAS notices that discuss the intended use of *M. alpina* oil in infant formulas.[3] Cultures are fermented in nutrient-rich broth containing glucose and yeast powder under axenic conditions. The resulting ARA-rich biomass is filtered, dried, and extracted with butane to yield crude *M. alpina* oil. After evaporation of the solvent, the crude oil is degummed (optional step), neutralized with alkali solution, and separated by centrifugation. The oil is then standardized with sunflower oil and treated with antioxidants (tocopherols and/or ascorbyl palmitate) before further processing. The oil is bleached using bleaching earth and activated carbon, and then subjected to filtration and deodorization using standard procedures. Residual volatile components are removed by deodorization. Optionally, a distillation step may be applied, as needed, to remove excess free fatty acids and sterols. BASF states that *M. alpina* oil is produced in accordance with current good manufacturing practices. BASF further notes that growth media, raw materials, and processing aids used in the fermentation and manufacturing processes are food-grade.

BASF provides specifications for *M. alpina* oil that include minimum content of ARA (≥40% weight basis) and limits for acid value (≤1.0 mg potassium hydroxide/g), free fatty acids (≤0.2%), peroxide value (≤2.0 milliequivalents (meq)/kg), anisidine value (≤20), unsaponifiable matter (≤3.0%), lead (<0.02 mg/kg), and microorganisms, including *Salmonella* sp. (negative in 25 g). BASF states that the manufacturing process will eliminate *Enterobacteriaceae* and provides batch data to demonstrate that *Cronobacter sakazkii* is not present. Quality specifications are consistent with those stated in the 12th edition of the Food Chemicals Codex (FCC, 2021) for ARA from Fungal (*Mortierella alpina*) Oil. BASF provides the results of six non-consecutive batch analyses (three from each production strain) of the oil to demonstrate that the ingredient can be manufactured to meet these specifications.

BASF estimates the dietary exposure to ARA from the intended use 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

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[1] In comparison to the Food Chemicals Codex 12th edition (FCC, 2021) monograph for ARA from Fungal (*Mortierella alpina*) Oil, the *M. alpina* oil in GRN 000963 contains higher levels of oleic acid and, to a lesser extent, palmitic and stearic acids, and lower levels of lignoceric and behenic acids. BASF states that the differences in the content of these fatty acids do not affect its safety conclusion.

[2] BASF states that both production strains of *M. alpina* are wild-type and non-toxigenic. *M. alpina* strain XM027 is deposited at the CGMCC (China General Microbiological Culture Collection Center) under registry number 21451. *M. alpina* strain CNCM I-4642 is registered in the Collection Nationale de Cultures de Microorganismes (CNCM, France) and it is deposited at the China Center for Type Culture Collection (CCTCC, China) under registry number M 209116.

[3] ARA-containing *M. alpina* oil, in combination with a safe and suitable source of DHA, was the subject of GRNs 000041, 000080, 000094, 000326, and 000730. We evaluated these notices and responded in letters dated May 17, 2001; December 11, 2001; April 18, 2006; October 24, 2010; and March 30, 2018, respectively, stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

comprises 50% of the available energy in human milk or infant formula, (3) pre-term infants consume 6.7 g fat/kg bw/d and term infants consume 5.6 g fat/kg bw/d, and (4) body weights of pre-term and term infants are 2 kg and 3.5 kg, respectively. The estimated mean dietary exposures to ARA are 27 mg/kg bw/d for pre-term infants and 45 mg/kg bw/d for term infants. BASF notes that its use levels and estimates of dietary exposure to ARA are consistent with those reported in previous GRNs (GRN 000326, GRN 000730).[4]

BASF discusses data and information supporting the safety of *M. alpina* oil and states an updated literature search conducted through May 2020, for both infant and adult consumers, did not identify any concerns for potential adverse health effects. BASF states the *M. alpina* oil has a lipid (fatty acid and sterol) profile generally similar to other ARA-containing oils from *M. alpina* previously concluded to be GRAS for their intended uses. BASF further states that any minor differences in fatty acids and sterols do not affect the safety conclusion. Thus, BASF incorporates safety studies, clinical studies, and information on the metabolic fate of ARA from GRNs 000041, 000080, 000094, 000326, and 000730.[3] BASF provides a summary of published studies describing the metabolic fate of ARA and discusses published preclinical studies including mutagenicity and genotoxicity studies, acute and subchronic toxicity studies in rats and piglets, and developmental and reproductive toxicology studies in rats to support the safe use of *M. alpina* oil. BASF also provides a specific discussion of published clinical studies in infants from GRNs 000326 and 000730 and summarizes the results of more recent published clinical studies in pre-term and term infants to support the safety of ARA supplementation of infant formula.

Based on the totality of the data and information, BASF concludes that *M.alpina* oil is GRAS for its intended 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 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 the ONFL in CFSAN. The 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 Formulas

Under section 412 of the FD C Act, a manufacturer of a new infant formula must make

[4] GRNs 000326 and 000730 both addressed the use of *M. alpina* oil in pre-term and term infant formula at levels providing, respectively, up to 0.4% and 0.75% of fat as ARA.

a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to BASF'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 the ONFL in CFSAN.

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 BASF'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 BASF provided, as well as other information available to FDA, we have no questions at this time regarding BASF'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 000963 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S
Digitally signed by Susan J. Carlson -S
Date: 2021.10.19 18:14:41 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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