



James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach, LLC
P.O. Box 66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000809

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000809. We received the notice that you submitted on behalf of Arla Foods Ingredients Group P/S (Arla) on August 22, 2018,¹ and filed it on October 9, 2018. Arla submitted amendments to the notice on December 20, 2018, February 1, 2019, March 8, 2019, and April 3, 2019, that provided additional information on the intended use, identity, composition, and manufacturing.

The subject of the notice is fractionated whey protein concentrate containing 41% alpha-lactalbumin (fractionated WPC (41% ALA)) for use as an ingredient in cow's milk-based, non-exempt infant formula for term infants at a level up to 8.3 g/L. The notice informs us of Arla's view that this use of fractionated WPC (41% ALA) is GRAS through scientific procedures.

Our use of the term, "fractionated whey protein concentrate containing 41% alpha-lactalbumin" or "fractionated WPC (41% ALA)," 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 "fractionated whey protein concentrate containing 41% alpha-lactalbumin" or "fractionated WPC (41% ALA)."

Arla provides information about the identity and composition of fractionated WPC (41% ALA). The main protein component is ALA, which consists of a single polypeptide chain

¹ Arla submitted an update to the notice on September 27, 2018 that clarified the intended infant formula type and infant population.

of 123 amino acids and a molecular weight of 14.2 kDa. Arla notes that the fractionated WPC (41% ALA) contains higher levels of ALA (41-52% of total protein) and lower levels of β -lactoglobulin (<23%) than whey protein concentrate defined in 21 CFR 184.1979c. Other proteins present in fractionated WPC (41% ALA) include β -lactoglobulin (~19%), casein glycomacropeptide (~16%), and minor amounts of β -casein-derived peptides.

Arla describes the method of manufacture for fractionated WPC (41% ALA). Arla describes the sweet whey starting material produced from pasteurized fluid milk as a byproduct of cheesemaking. Sweet whey is food-grade and produced in accordance with current good manufacturing practices. The sweet whey starting material is clarified and pasteurized a second time before production of fractionated WPC (41% ALA). Arla describes the production as a two-stage ultrafiltration process to increase the ratio of ALA to β -lactoglobulin. Fractionated WPC (41% ALA) may be standardized with food-grade lactose (targeted percent dry matter) or pH-adjusting agents (NaOH or HCl) prior to spray drying. Arla states that all membrane materials are safe and suitable for their intended use and are used in accordance with regulations for food contact materials.

Arla provides specifications for fractionated WPC (41% ALA), including levels of protein (81.0-87.0%), ALA as a percent of protein (\geq 41.0%), ash (\leq 5.0%), moisture (\leq 5.5%), lactose (\leq 10.0%), fat (\leq 2.0%), calcium (0.40-0.60%), phosphorous (0.20-0.40%), sodium (0.20-0.45%), chloride (\leq 0.20%), potassium (0.50-0.90%), heavy metals (<0.2 mg/kg arsenic and <0.05 mg/kg for cadmium, lead, and mercury), and limits for microorganisms, including *Salmonella* serovars (absent/25 g sample) and *Cronobacter sakazakii* (absent/10 g sample). Arla presents results of five non-consecutive batch analyses to demonstrate that fractionated WPC (41% ALA) can be manufactured to meet these specifications.

Arla estimates the dietary exposure to fractionated WPC (41% ALA) based on a target ALA concentration of 2.5 g/L infant formula, standard energy density of infant formula for term infants (67.6 kcal/100 mL), and published values for 90th percentile energy intakes of formula-fed term infants. Using the midpoint for 90th percentile intakes of infant formula for male and female infants (207 mL/kg/d) and a use level of 8.3 g/L of fractionated WPC (41% ALA), the estimated daily exposure to fractionated WPC (41% ALA) at the 90th percentile is 1.72 g/kg body weight/day. Fractionated WPC (41% ALA) is intended to replace WPC in infant formula for term infants. Infant formulas contain variable levels of whey and casein depending on the manufacturer. Arla estimates that fractionated WPC (41% ALA) will replace 44% (for 70:30 whey:casein formulas) to 100% (for 50:50 whey:casein formulas) WPC to achieve the target level of 2.5 g/L of ALA in infant formula. Arla also provides a comparison of the amino acid composition of WPC and fractionated WPC (41% ALA).

Arla discusses the safety of fractionated WPC (41% ALA). ALA is the predominant whey protein in mature human milk (>1-month lactation). In bovine milk, less ALA is present as a percent of total whey protein and β -lactoglobulin predominates. Arla states that tryptophan (Trp) is the limiting amino acid in low-protein infant formulas. This is mainly due to lower ALA content in cow's milk whey as compared to human milk protein. Citing several published studies in human infants, as well as infant monkeys,

Arla states that higher levels of fractionated WPC (41% ALA) in the formula increased plasma Trp levels, supported normal growth, and resulted in no toxicologically relevant effects.

Arla includes the statement of a panel of individuals (Arla's GRAS panel). Based on its review, Arla's GRAS panel concluded that fractionated WPC (41% ALA) is safe under the conditions of its intended use.

Based on the totality of evidence, Arla concludes that fractionated WPC (41% ALA) 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). The notice raises a potential issue under these labeling provisions. In the notice, Arla cites studies that describe fractionated WPC (41% ALA) as having certain health benefits. If products containing fractionated WPC (41% ALA) 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 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. Fractionated WPC (41% ALA) derived from milk requires labeling under the FD&C Act because it contains protein derived from cow's milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. Questions related to food labeling in general 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 a submission to FDA providing required assurances about the formula at least 90 days before the formula is marketed. Our response to Arla's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing fractionated WPC (41% ALA) 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 Arla's notice concluding that fractionated WPC (41% ALA) 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 fractionated WPC (41% ALA). Accordingly, our response should not be construed to be a statement that foods containing fractionated WPC (41% ALA), if introduced or delivered for introduction into interstate commerce, would not violate section 301(II).

Conclusions

Based on the information that Arla provided, as well as other information available to FDA, we have no questions at this time regarding Arla's conclusion that fractionated WPC (41% ALA) is GRAS under its intended conditions of use. This letter is not an affirmation that fractionated WPC (41% ALA) 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 000809 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,
Michael A.

Adams -S

Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

Digitally signed by Michael A.
Adams -S

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