Richard F. Mann
Keller and Heckman, LLP.
1001 G Street, N.W.
Suite 500 West
Washington, D.C. 20001

Re: GRAS Notice No. GRN 000763

Dear Mr. Mann,

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000763. We received the notice that you submitted on behalf of Agropur, Inc. (Agropur) on February 27, 2018, and filed it on April 3, 2018. Agropur submitted amendments to the notice on August 21, 2018, and October 1, 2018, providing additional information on the identity, method of purification, specifications, batch analyses, and estimated dietary exposure of α-lactalbumin.

The subject of the notice is α-lactalbumin for use as a protein source and/or texturizer in powdered meal replacement or meal supplement beverages (at levels up to 20% w/w powder), sports beverages (at levels up to 20% w/w), meal replacement or snack bars (at levels up to 25% w/w), and milk products (including dairy beverages, at levels up to 10% w/w), intended only for use in these foods where permitted by applicable standards of identity. The notice informs us of Agropur's view that this use of α-lactalbumin is GRAS through scientific procedures.

Agropur cites published references that characterize the identity of α-lactalbumin, a protein that comprises 20-30% of the whey protein fraction of cow's milk; whey typically comprises 20% of total milk proteins. The CAS No. for α-lactalbumin is 9051-29-0, and the molecular weight is approximately 14 kiloDaltons. α-Lactalbumin is a metalloprotein composed of 123 amino acids. α-Lactalbumin binds calcium and other cations. The isoelectric point ranges from 4.2-4.5.

Agropur states that α-lactalbumin is isolated from skim milk or whey using physical separation techniques including ultrafiltration and microfiltration processes analogous to those described in GRN 000504 for milk protein concentrate and milk protein isolate and those described in GRN 000633 for concentrated milk protein with ≥60:40 whey:casein ratio. α-lactalbumin is obtained from one of two food-grade starting materials. The first potential starting material is sweet whey (21 CFR 184.1979) produced as a byproduct of the cheese-making process. The second is "milk-derived whey," obtained by membrane filtration and acidification of fluid milk ("milk-derived whey"). Microfiltration may be used to further remove fat from the whey fraction. The whey is then subjected anion exchange chromatography to remove lactose, minerals,

and certain proteins (e.g., lactoferrin, lactoperoxidase). α-Lactalbumin is further purified by selective precipitation with a salt solution followed by removal of extraneous proteins (e.g., β-lactoglobulin) by centrifugation. The resulting α-lactalbumin is further concentrated using ultrafiltration and diafiltration to remove water, salt, minerals, and other low molecular weight constituents. Agropur notes that all filtration and ion-exchange materials comply with applicable food contact regulations, including 21 CFR 177.2910 ultrafiltration membranes and 21 CFR 173.25 ion-exchange resins. In addition to membrane filtration processes, isolation of α-lactalbumin also includes pH adjustment and ion-exchange chromatography. The pH and ionic strength of the liquid whey are adjusted with food-grade acid and salts (sodium, potassium, or calcium chloride). The product, liquid α-lactalbumin, is pH adjusted with food-grade sodium hydroxide. The final product is spray-dried, producing a white to light cream-colored powder. Agropur notes that the typical composition of their α-lactalbumin is 90-96% α-lactalbumin protein, 3-5% beta-lactoglobulin, 0-5% bovine serum albumin, and 0-2% immunoglobulin G. Regardless of the starting material used, the whey is pasteurized in accordance with the requirements of the Pasteurized Milk Ordinance (PMO, 2011; 21 CFR 1240.61), and the α-lactalbumin is produced in accordance with current good manufacturing practices.

Agropur provides specifications and typical composition of α-lactalbumin. Food-grade α-lactalbumin contains a minimum of 95.0% (w/w basis) protein; with a minimum of 90.0% (w/w basis) of that protein comprised of α-lactalbumin. Agropur also provides specifications for fat (not more than (NMT) 0.5%), ash (NMT 3.5%), lactose (NMT 0.2%), and pH (6.0-7.5). Agropur provides results of batch analyses (n=6), demonstrating compliance with specifications. In general Agropur's α-lactalbumin meets the specifications for α-lactalbumin monographed in the Food Chemicals Codex (FCC 11th edition, 2016). However, batch analyses indicate a slightly higher range for calcium (0.85-2.38 mg/g) than specified by FCC 11 (NMT 1 mg/g). Additionally, Agropur has set limits for microorganisms and meets the FCC 11th edition limits for lead (≤0.5 mg/kg) and β-lactoglobulin (NMT 6.5% of protein).

Agropur notes that α-lactalbumin may be used as a substitute for whey protein concentrates and whey protein isolates to provide texture and as a protein source, while providing enhanced heat stability. While we do not question Agropur's statement about substitution for whey protein concentrates/isolates, we do not concur with Agropur's use of micellar casein as a proxy for estimating background dietary exposure to whey protein or whey protein fractions. Further, given the limitations of using poundage data for specific food uses at levels of use intended to boost intake of a specific protein, we estimated the dietary exposure of α-lactalbumin based on the intended use levels in the notice, and consumption data from the National Health and Nutrition Examination Survey 2009-2014. Assuming that α-lactalbumin is added at 10% to dairy beverages, 25% to nutrition bars,[1] and 20% to sports beverages, nutritional beverages, and

[1] Agropur considers "nutritional bars" and "nutritional beverages" among the intended uses. For estimating exposure to "nutritional" food and beverages, FDA includes consumption data for the following foods: milk-based meal replacements, powdered beverage mixes with dry milk, breakfast bars, certain snack bars, weight-loss/meal replacement bars, nutritional drinks and shakes (ready to drink or powder).

beverages prepared from premixes,[2] we estimate the mean consumption for users only (27.5% of population ages 1+ y) is approximately 36 g/p/d at the mean and 74 g/p/d at the 90th percentile, noting recommended intakes for protein from the Institute of Medicine.[3]

Agropur describes the safety of α-lactalbumin by noting that several substances that are similar to α-lactalbumin have already been affirmed as GRAS under certain conditions of use (whey protein concentrate (21 CFR 184.1979(c)) and casein peptones (21 CFR 184.1553)) or have been the subject of previous GRAS notices.[4] In addition, Agropur incorporates the safety overview provided in GRN 000504 into GRN 000763 considering the substantial similarities between α-lactalbumin and traditional whey protein, as well as that the concentrated milk proteins that have been the subject of GRN 000504. Agropur notes that milk and milk-derived products, such as whey, have a long history of safe consumption by humans at all ages in the form of fluid milk, in dried form (i.e., milk powder), or as milk-derived ingredients with no toxicological concern except for the milk-allergic and lactose-intolerant individuals. With respect to lactose intolerance, Agropur states that the percentage of lactose is inversely related to the protein content, so as the protein content increases, the lactose level decreases. Agropur reports that the percentage of lactose in α-lactalbumin products is <0.2% which is an order of magnitude lower than that in nonfat dry milk and therefore, do not anticipate any adverse effects on lactose sensitive populations.

Based on the information described above, Agropur concludes that α-lactalbumin produced in accordance with cGMP and meeting appropriate food grade specifications, is GRAS for its intended use in food.

Standards of Identity

In the notice, Agropur states its intention to use α-lactalbumin in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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.

Allergen Labeling

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[2] In the absence of specific information on composition of reconstituted beverages, FDA used the 20% level specified for sports drinks in preparing its estimate.

[3] Recommended dietary allowances for protein established by the Institute of Medicine: 56 g/p/d for adult males and 46 g/p/d for adult females.

[4] FDA evaluated GRN 000011 (a mixture of calcium casein peptone and calcium phosphate), GRN 000037 (whey protein isolate), GRN 000052 (whey mineral concentrate), GRN 000196 (bovine milk basic protein fraction), GRN 000504 (milk protein concentrate and milk protein isolate), and GRN 000633 (whey protein consisting of concentrated milk protein (whey: casein ≥ 60:40)) and responded in letters dated January 29,1999, April 21, 2000, January 30, 2001, September 1, 2006, November 21, 2014, and September 30, 2016, respectively, stating that we had no questions at that time regarding the notifier's GRAS conclusions.

The Federal Food, Drug, and Cosmetic Act (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. α-Lactalbumin requires labeling under the FD&C Act because it contains protein derived from milk

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 Agropur's notice concluding that α-lactalbumin 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 α-lactalbumin. Accordingly, our response should not be construed to be a statement that foods containing α-lactalbumin, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Agropur provided, as well as other information available to FDA, we have no questions at this time regarding Agropur's conclusion that α-lactalbumin is GRAS under its intended conditions of use. This letter is not an affirmation that α-lactalbumin 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 000763 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

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