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February 26, 2018

Via FedEx

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Campus Drive
College Park, MD 20740

Re: GRAS Notice for Alpha-Lactalbumin

Dear Sir or Madam:

We respectfully submit the enclosed GRAS notice (in electronic format, *i.e.*, CD) on behalf of our client, Agropur, Inc. (Agropur), in support of this notice that alpha-lactalbumin – one of the four major whey proteins naturally present in cow's milk – is generally recognized as safe (GRAS) for use in multiple food applications. The enclosed GRAS notice provides detailed information related to the intended uses, manufacturing, and safety of alpha-lactalbumin.

We look forward to FDA's review of this submission and would be happy to answer any questions. If any questions do arise, please contact me at (202) 434-4229 so that we can respond as quickly as possible.

We appreciate your assistance and look forward to receiving additional feedback.

Sincerely,

(b) (6)

Richard F. Mann
Natalie E. Rainer

Enclosures: (1) CD and (2) paper copy

GRN 000763

GRAS Notice for Alpha-Lactalbumin

U.S. Food and Drug Administration
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
4300 River Road
College Park, MD 20740

Prepared by: Keller and Heckman LLP
1001 G Street, NW
Suite 500W
Washington, DC 20001

Date: February 26, 2018

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I. Signed Statements and Certification (21 C.F.R. § 170.225)

In accordance with Subpart E ("Generally Recognized as Safe (GRAS) Notice") of 21 C.F.R. Part 170 ("Food additives"), Keller and Heckman LLP submits the enclosed information on behalf of our client, Agropur, Inc., in support of this notice that alpha-lactalbumin – one of the four major whey proteins naturally present in cow's milk – is generally recognized as safe (GRAS) for use in multiple food applications.

Alpha-lactalbumin is intended for use as a food ingredient for functional or nutritional purposes in the following foods: Powdered Nutritional Beverages (at up to 20% w/w), Sports Beverages (at up to 20% w/w), Nutritional Bars (at up to 25% w/w), and Milk Products (including dairy beverages, at up to 10% w/w). This substance is intended to serve as a source of high-quality protein and/or a texturizer. Foods containing alpha-lactalbumin will be consumed by the general population (children over one year and adults).

Agropur, Inc., has determined that alpha-lactalbumin is GRAS for use in a variety of food categories based on scientific procedures in accordance with Section 170.30(a) and (b), and in conformance with the GRAS final rule published by FDA on August 17, 2016, 81 Fed. Reg. 54960. Given the determination that alpha-lactalbumin is GRAS for the intended uses described herein, it is our view that premarket approval required under the Federal Food, Drug, and Cosmetic Act (FD&C Act) is not required.

The analytical data, published studies, and information that are the basis for this GRAS determination are available for FDA review and copying at reasonable times at Keller and Heckman LLP, 1001 G Street, NW, Suite 500W, Washington, DC 20001, or will be sent to FDA upon request.

A. Name and Address of the Notifier

Agropur, Inc.
3500 E. Destination Drive
Appleton, Wisconsin 54915

All communications on this matter are to be sent to Counsel for the Notifier:

Richard F. Mann
Keller and Heckman LLP
1001 G Street, NW
Suite 500W
Washington, DC 20001
Telephone: (202) 434-4229
Facsimile: (202) 434-4646
Email: mann@khlaw.com

B. Certification

I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as

favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance

Signature:

(b) (6)

Richard F. Mahn
Counsel to Agropur, Inc.

Date: February 26, 2018

II. Identity, method of manufacture, specifications, and physical or technical effect (21 C.F.R. § 170.230)

Alpha-lactalbumin (Chemical Abstracts Service Registry Number (CASRN) 9051-29-0) is one of the four major whey proteins present in cow's milk, constituting approximately 20-30% of the overall protein content contributed by the whey proteins present in milk. It is isolated and purified from milk or whey (using physical separation techniques including ion exchange and membrane processing) and then concentrated and spray-dried. Once processed, it is a homogenous, semi-hygroscopic white to light cream colored powder.

A. Manufacturing Process

The manufacturing process for alpha-lactalbumin involves physical processing techniques to isolate alpha-lactalbumin from whey. The process, which is similar to those described in GRN000504 (Milk Protein Concentrate, Milk Protein Isolate) and GRN000633 (Concentrated Milk Protein with $\geq$60:40 whey:casein ratio"), uses a combination of existing dairy production techniques—including Ion Exchange, Membrane Separation, and Centrifugal Separation. Alpha-lactalbumin is manufactured in accordance with Hazard Analysis and Risk-Based Preventive Controls and Good Manufacturing Practices for food, consistent with 21 C.F.R. Part 117.

To produce alpha-lactalbumin, fresh sweet dairy whey from the cheese manufacturing process is clarified to remove cheese fines and skimmed to remove whey fat. As an alternative to dairy whey from cheese manufacturing, a purified whey protein solution may be used.[1]

To ensure pathogen control and compliance with regulatory requirements, the clarified and separated liquid sweet dairy whey is pasteurized in accordance with Pasteurized Milk Ordinance (PMO) requirements. Specifically, the product is pasteurized using High Temperature Short Time (HTST) at a minimum temperature of 161°F for a minimum of 15 seconds.

Techniques used to concentrate protein and ensure highly purified protein include a combination of ion exchange, membrane filtration, and centrifugal separation. All food-contact membrane materials employed in the production of alpha-lactalbumin comply with applicable food-contact regulations (*e.g.*, 21 C.F.R. § 177.2910) ("Ultra-filtration membranes"). Major whey proteins are fractionated by ion exchange to remove extraneous components, resulting in a purified liquid protein.

The pH and ionic strength of the purified whey protein liquid is adjusted using food-grade acid and food-grade salts (e.g., sodium chloride and/or potassium chloride and/or calcium chloride). Any food-grade acids and salts used in the processing of alpha-lactalbumin are either GRAS for their intended use or the subject of applicable food additive regulations.

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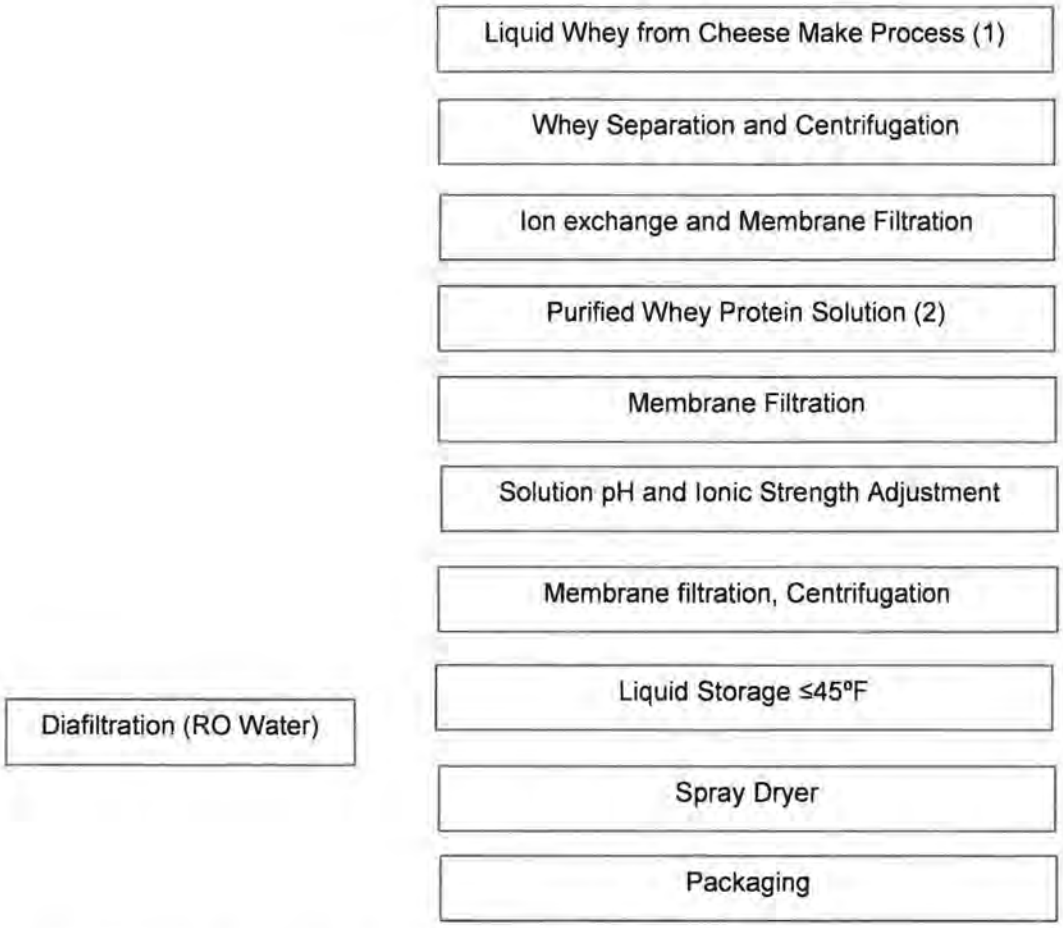
[1] This process involves acidifying and heat-treating fresh milk. An organic solvent is added, and insoluble protein precipitates out of solution. Alpha-lactalbumin remains soluble in the whey protein solution.

The solution is processed with centrifugal separation to selectively purify alpha-lactalbumin from the whey protein solution. The concentrated alpha lactalbumin liquid is further purified by membrane filtration (incorporating diafiltration) to remove water, food-grade salts, other minerals, and low molecular weight constituents from the final product, resulting in a highly-purified alpha-lactalbumin liquid. The final product is pH adjusted with sodium hydroxide meeting the specifications under 21 C.F.R. § 184.1763. The solution is further concentrated with membrane equipment to remove water. The typical composition of protein in the finished product is 90-96% alpha-lactalbumin, 3-5% beta-lactoglobulin, 0-5% bovine serum albumin, and 0-2%, and immunoglobulin G 0-2%.

The concentrated liquid is stored at 45°F or less, followed by spray drying (using normal dairy drying techniques) prior to packaging.

A manufacturing process flow chart is provided below in **Figure 1**.

Figure 1. Manufacturing Process Flow Chart



(1) Start of process if using Whey from Cheese Making.

(2) Start of process if using alpha-lactalbumins isolated directly from Milk.

B. Product Specifications

Agropur provides compositional and microbiological specifications for its alpha-lactalbumin, as summarized in **Tables 1** and **2** below.

Table 1. Compositional Specifications

Parameter	Specification	Method
Moisture (%)	≤6.0	Vacuum Oven AOAC 927.05
Protein, Dry Basis (N*6.25, %)	≥95.0	Leco Combustion AOAC 990.03
Alpha-lactalbumin (% of protein)	≥90.0	HPLC-USP NF
Fat (%)	≤0.5	Mojonnier AOAC 989.05
Ash (%)	≤3.5	Residue on Ignition AOAC 930.30
Lactose (%)	≤0.2	Enzymatic AOAC 984.15
pH	6.0-7.5	10% Sol. @ 20C, AOAC 945.27
Scorched Particles, mg/25g	≤15.0	ADPI, AOAC 952.21

Table 2. Microbiological Specifications

Parameter	Specification	Method
Aerobic Plate Count/g	<10,000	FDA/BAM, AOAC 966.23
Coliform (MPN)/g	<10	FDA/BAM, AOAC 966.23
E.coli (MPN)/g	Negative	FDA/BAM, AOAC 966.23
Yeast & Mold/g	≤10	FDA/BAM
Coagulase-Positive *Staphylococcus* (MPN)/g	<10	FDA/BAM, AOAC 966.23
Salmonella sp./375g	Negative	FDA/BAM, ELISA AOAC 2004.03
Listeria sp./25g	Negative	FDA/BAM, ELISA AOAC 999.06

Five batch analyses demonstrating compliance with specifications are provided below.

Table 3. Product Analysis

Parameter	Specification	Batch 1 JE 015-6-414	Batch 2 JE 024-6-414	Batch 3 JE 001-7-414	Batch 4 JE 008-7-414	Batch 5 JE 010-7-414
Moisture	<6.0	5.4	5.4	4.9	5.4	4.9
Protein, Dry basis	≥95.0	97.6	98.1	97.3	98.1	97.2
Alpha-lactalbumin (% of protein)	>90.0	91.7	92.6	93.9	92.6	90.1
Fat (%)	<0.5	0.1	0.1	0.1	0.1	0.1
Ash (%)	<3.5	2.2	1.7	2.4	1.7	2.6
Lactose (%)	<0.2	0.0	0.0	0.0	0.0	0.0
pH	6.0-7.5	6.3	6.0	6.5	6.0	6.8
Scorched Particles (mg/25 g)	≤15.0	7.5	7.5	7.5	7.5	7.5
Aerobic Plate Count (per gram)	<10,000	<250	<250	<250	<250	<250

Parameter	Specification	Batch 1 JE 015-6-414	Batch 2 JE 024-6-414	Batch 3 JE 001-7-414	Batch 4 JE 008-7-414	Batch 5 JE 010-7-414
Coliform (MPN/g)	<10	<10	<10	<10	<10	<10
E. coli (MPN/g)	Negative	Negative	Negative	Negative	Negative	Negative
Yeast & Mold (per gram)	≤10	<10	<10	<10	<10	<10
Coagulase-Positive *Staphylococcus* (MPN/g)	<10	<10	<10	<10	<10	<10
Salmonella sp. (per 375 g)	Negative	Negative	Negative	Negative	Negative	Negative
Listeria sp. (per 25 g)	Negative	Negative	Negative	Negative	Negative	Negative

C. Physical and Technical Effect

The value of the protein digestibility-corrected amino acid score (PDCAAS) for whey protein derived from cheese making has been shown to be 1.14, higher than for beef (0.9), soy (0.93) or wheat (0.42).[2] Because alpha-lactalbumin will be obtained from either whey from cheese making or directly from milk, the PDCAAS for alpha-lactalbumin is expected to be equivalent to whey protein derived from cheese making.

Agropur has conducted testing using the Digestible Indispensable Amino Acid Score (DIAAS), an alternative to PDCAAS, for testing protein quality that has been recommended by the Food and Agriculture Organization (FAO) of the United Nations.[3] A DIAAS measurement was performed at the Riddet Institute at Massey University, New Zealand using standard protocols previously reviewed and published. The DIAAS score for alpha-lactalbumin was determined to be well over 100, indicating complete amino acid availability.

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[2] Schaafsma G. The Protein Digestibility-Corrected Amino Acid Score. J Nutr 2000; 130:1865S-1867S (internal citations omitted).

[3] *See* Dietary protein quality evaluation in human nutrition: Report of an FAO Expert Consultation, FAO Food and Nutrition Paper 92 (FAO, 2013). *See also* Rutherford *et al.*, Protein digestibility-corrected amino acid scores and digestible indispensable amino acid scores differentially describe protein quality in growing male rats. J Nutr. 2015 Feb;145(2):372-9. 2014 Nov 26, summary available at https://www.ncbi.nlm.nih.gov/pubmed/25644361 (last accessed November 28, 2017). We note that FAO has decided to continue recommending PDCAAS testing in follow-up formula. *See* Joint FFAO/WHO Food Standards Programme Codex Committee on Nutrition and Foods for Special Dietary Uses, Thirty-Eighth Session (Hamburg, Germany, 5 – 9 December 2016), Review Of The Standard For Follow-Up Formula (Codex Stan 156-1987), Physical Working Group Report, at http://www.fao.org/fao-who-codexalimentarius/sh-proxy/es/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-720-38%252FCRDs%252FCRD_13.pdf (last accessed November 28, 2017).

The nutritional utilization of milk proteins has been studied in both animals and humans.[4] It has been shown that milk proteins are of particularly excellent nutritional value in humans with a true digestibility and a net postprandial protein utilization of 95-96% and 74%, respectively.[5]

D. Consideration of Potential Contaminating Materials

1. Pesticide Residues

Agropur screens its alpha-lactalbumin biannually for agricultural residues using Multi Residue Methods (MRM) for common pesticides, insecticides, herbicides, and fungicides (including organochlorides, organophosphates, organonitrogen, carbamates and pyrethroids). Historical MRM screening have not indicated unlawful residues in Agropur products, including alpha-lactalbumin.

2. Melamine

Alpha-lactalbumin is screened biannually to verify the absence of melamine. The results show that melamine is not present in this product. All equipment used in the manufacturing of this product and its packaging materials are melamine free. Agropur uses FDA's method described in Laboratory Information Bulletin (LIB) 4422 ("Melamine and Cyanuric Acid Residues in Foods") to test for melamine.

3. Drug Residues

The milk used in the production of alpha-lactalbumin is tested for drug residues as described under Appendix N of the PMO, per procedures for sampling, analysis, and reporting described therein.[6] The document states "industry shall screen all bulk milk pickup tankers, regardless of final use, for Beta lactam drug residues. Additionally, other drug residues shall be screened for by employing a random sampling program on bulk milk pickup tankers when the Commissioner of the FDA determines that a potential problem exists as cited in [Section 6 of the PMO]. The random bulk milk pickup tanker sampling program shall represent and include, during any consecutive six (6) months, at least four (4) samples collected in at least four (4)

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[4] Cook BB, Morgan AF, Singer B, Parker J. The effect of heat treatment on the nutritive value of milk proteins. II. Rat growth studies with casein and lactalbumin and their lactose derivatives. J Nutr 1951;44:63–81; Gilani GS, Sepehr E. Protein digestibility and quality in products containing antinutritional factors are adversely affected by old age in rats. J Nutr 2003;133:220–5; Rutherfurd SM, Moughan PJ. The digestible amino acid composition of several milk proteins: application of a new bioassay. J Dairy Sci 1998; 81:909–17; Bos C, Gaudichon C, Tome D. Nutritional and physiological criteria in the assessment of milk protein quality for humans. J Am Coll Nutr 2000;19(suppl):191S–205S; Gaudichon C, Mahe S, Benamouzig R, *et al.* Net postprandial utilization of [15N]-labeled milk protein nitrogen is influenced by diet composition in humans. J Nutr 1999;129:890–5.

[5] Bos C, Mahe S, Gaudichon C, *et al.* Assessment of net postprandial protein utilization of 15N-labelled milk nitrogen in human subjects. Br J Nutr 1999;81:221–6; Bos C, Metges CC, Gaudichon C, *et al.* Postprandial kinetics of dietary amino acids are the main determinant of their metabolism after soy or milk protein ingestion in humans. J Nutr 2003;133:1308–15; Gausseres N, Mahe S, Benamouzig R, *et al.* [15N]-labeled pea flour protein nitrogen exhibits good ileal digestibility and postprandial retention in humans. J Nutr 1997;127:1160–5; Morens C, Bos C, Pueyo ME, *et al.* Increasing habitual protein intake accentuates differences in postprandial dietary nitrogen utilization between protein sources in humans. J Nutr 2003;133:2733–40.

[6] FDA, Grade "A" Pasteurized Milk Ordinance (2013 Revision), at Appendix N ("Drug Residue Testing and Farm Surveillance – Industry Responsibilities – Monitoring and Surveillance").

separate months, except when three (3) months show a month containing two (2) sampling dates separated by at least twenty (20) days. Samples collected under this random sampling program shall be analyzed as specified by FDA." The Notifier follows PMO guidelines with respect to monitoring for contaminants during the production of alpha-lactalbumin.

III. Estimated Consumption of Alpha-Lactalbumin (21 C.F.R. § 170.235)

Alpha-lactalbumin is intended for use as a food ingredient for functional (texturizer) or nutritional (high-quality protein) purposes in Nutritional Products and Dairy and Dairy-Based Products. Specifically, alpha-lactalbumin is intended for use at up to 20% w/w in Powdered Nutritional Beverages and Sports Beverages, 25% w/w in Nutritional Bars, and 10% w/w in Milk Products (including dairy beverages).

Due to the relative novelty of high purity alpha-lactalbumin products, specific consumption data are not available at this time. However, because alpha-lactalbumin products are equivalent to traditional whey protein products from the standpoint of nutritional properties and safety, and because alpha-lactalbumin products effectively will substitute for traditional whey protein products in the marketplace, we anticipate no issues related to dietary exposure.

As a conservative numeric estimate, we have calculated dietary exposure using data available for an analogous dairy protein product, micellar casein. In 2010 the total domestic market for micellar casein (all protein levels) was estimated to be 5,000 metric tons (5.0×10^6 kg).[7] The total population of the United States in 2010 was about 310 million people.[8] The mean daily consumption of micellar casein per capita is as follows:

$$5.0 \times 10^6 \text{ (kg/year)} \times 10^3 \text{ (g/kg)} \div 310 \times 10^6 \text{ (persons)} \div 365 \text{ (days/year)} = 0.044 \text{ g/person/day}$$

We conservatively assume that the protein content of the micellar casein comprises 90% of the product. The mean daily protein intake from micellar casein per capita would thus be:

$$0.044 \text{ g/person/day} \times 90\% = 0.040 \text{ g/person/day}$$

If we assume that the entire amount of micellar casein produced in the United States is consumed by only 10% of the population ("eaters-only"), the daily consumption of micellar casein per capita for the eaters-only population would be 0.44 g/person/day, and the daily protein intake from micellar casein per capita would thus be 0.40 g/person/day. **Table 4** provides recommendations for milk intake taken from GRN000504 for concentrated milk proteins:

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[7] Leprino Foods Company, GRN000633 regarding Whey Protein Concentrate, available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505250.pdf (last accessed November 28, 2017), citing DH Business Consulting and Associates, Micellar casein ingredients business & market analysis (2013).

[8] The 2017 population of the United States is slightly higher than this figure, but we have used a 2010 population estimate to remain conservative and consistent with the available market data for micellar casein.

Table 4. Recommendations for Milk Intake

Male and Female Age Groups	Number of 8 ounce cups per Day	Milk Protein Equivalent grams/daily
<1-3 years	1-2	8-16
4-8 years	2-3	16-24
9-18 years	4	32
19-50 years	3	24
51+ years	3	24

The recommended daily protein intake from milk for the general population, excluding infants, ranges between 8 and 32 grams per day, depending on age cohort. In addition, FDA has established a Daily Reference Value (DRV) of 50 g/day for protein for adults and children aged 4 or older.[9] The Institute of Medicine (IOM) has established a Recommended Dietary Allowance (RDA) for protein of 56 g/day for adult males and 46 g/day for adult females.[10] The estimated daily protein intake from micellar casein is approximately 0.040 g/person/day, which is a fraction of the recommended protein intake. Even considering the eaters-only population, which provides the most conservative estimate of consumption, the daily protein intake from micellar casein of 0.40 g/person/day is far less than the recommended protein intake described above. This data serves as a proxy for an alpha-lactalbumin consumption estimate, and they indicate there is no safety concern at the intended use levels.

Most of the population's protein intake is derived from, and will continue to be derived from unprocessed foods, including meat, poultry, fish, and legumes. Moreover, for those processed foods to which the alpha-lactalbumin will be added, there are competitive products on the market. Thus, the addition of alpha-lactalbumin simply will serve as a replacement for these other competitive protein sources and will not increase consumer exposure to protein. Therefore, we do not realistically expect that the actual consumption of foods containing alpha-lactalbumin will contribute to a significant portion of total protein intake.

IV. Self-Limiting Levels of Use (21 C.F.R. § 170.240)

The use of alpha-lactalbumin is not self-limiting. The maximum use levels in food are described above.

V. Experience based on common use in food before 1958 (21 C.F.R. § 170.245)

While the basis for this GRAS Notice is scientific procedures, rather than common use in food, we note that alpha-lactalbumin is a component of milk. Milk and products derived from milk, 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. Therefore, the

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[9] 21 C.F.R. § 101.9(c)(9)

[10] Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Total Water and Macronutrients. Food and Nutrition Board, Institute of Medicine, National Academies, available at https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t4/?report=objectonly (last accessed on November 28, 2017).

history of milk consumption provides supplemental support for the safety of alpha-lactalbumin's intended use.

VI. GRAS Notice Narrative (21 C.F.R. § 170.250)

As discussed further below, several substances that are similar to alpha-lactalbumin have already been affirmed as GRAS or have been the subject of GRAS Notices. Milk proteins are classified under two major groups: whey proteins (20%) and caseins (80%).[11] Whey proteins, in particular, are the soluble proteins that remain when milk coagulates. Like the GRAS substances described below, the alpha-lactalbumin that is the subject of the current GRAS Notice is manufactured through physical separation techniques. Therefore, the constituents of the final product are no different in substance than the other milk protein products described below. Due to the similarities between alpha-lactalbumin and the substances described below, FDA's acceptance of the GRAS status of the following substances has direct implications for the GRAS status of alpha-lactalbumin.

Whey protein concentrate is GRAS affirmed at 21 C.F.R. § 184.1979(c). The regulation states that whey protein concentrate is the substance obtained by the removal of sufficient non-protein constituents from whey so that the finished dry product contains no less than 25% total protein. Whey protein concentrate is produced by physical separation techniques, such as precipitation, filtration, or dialysis. As with whey, whey protein concentrate can be used as a fluid, concentrate, or dry product form.

In GRN000011, FDA had no questions regarding the GRAS determination of a "mixture of calcium casein peptone and calcium phosphate (CCP-CP)" for use as a texturizer in chewing gum at a level not to exceed 5%.[12] CCP-CP is produced by the enzymatic hydrolysis of casein to form casein peptone, which is then complexed with amorphous calcium phosphate to form a calcium casein peptone-calcium phosphate complex. Casein peptones have been GRAS affirmed for the direct addition to human foods at 21 C.F.R. § 184.1553.

In GRN000037, FDA had no questions regarding the GRAS determination of "whey protein isolate" for use in high-energy food and beverage products, such as yogurt, pudding, ice cream, margarine, and mayonnaise. Similarly, in GRN000037, FDA had no questions regarding the GRAS determination of "dairy product solids" for use in a variety of foods and in the production of alcohol and organic chemicals, galactose and glucose syrups, and sugar and corn syrup replacers. Both whey protein isolate and dairy product solids are manufactured using

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[11] *See, e.g.*, Institute of Food Technologists, Food Chemistry Experiments, IFT Experiments in Food Science Series, at page 3-1, available at http://www.ift.org/~/media/Knowledge%20Center/Learn%20Food%20Science/Experiments/TeacherGuidePROTEINS.pdf (last accessed on November 28, 2017).

[12] Bonlac Foods Limited, GRN000011 (regarding Calcium casein peptone-calcium phosphate), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264465.pdf (last accessed on November 28, 2017), and January 29, 1999 FDA Response to GRN000011, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154906.htm (last accessed on November 28, 2017).

physical separation techniques involving the application of membrane filtration systems and optional dialysis to process whey.[13]

In GRN000052, FDA had no questions regarding the GRAS determination of "whey mineral concentrate" for use as a source of calcium in fortified beverages, fortified foods, and enriched dairy products. Whey mineral concentrate is produced by subjecting pasteurized fluid whey to a precipitation and membrane separation process, followed by purification and drying. The resulting concentrate is a free-flowing white powder that is soluble at acid pH.[14]

In GRN000196, FDA did not object to the determination that "bovine milk basic protein fraction (BMBPF)" is GRAS for use in cottage cheese, imitation milk (including rice and soy milk), juice, meal replacement bars and drinks, milk, processed cheese, salad dressing, and yogurt at levels of up to 40% in some of the applications. BMBPF is produced from pasteurized bovine skim milk that is applied to a cation exchange chromatographic column, removing acid milk proteins and lactose. The basic proteins remaining on the column are eluted from the resin using sodium chloride. The resulting eluate is concentrated and dialyzed to produce BMBPF solids. These BMBPF solids are then crushed and packaged.[15]

In GRN000504, FDA had no questions regarding the GRAS determination related to "milk protein concentrate" containing 42 to 85% protein and "milk protein isolate" containing greater than 90% protein produced by ultrafiltration of skim milk.[16] The concentrated milk proteins described in GRN000504 were determined to be GRAS for use as ingredients in: meal replacements and meal supplements, milk products including milk drinks, yogurt, fermented milks, spreads, dips; non-standardized cheese products; dairy product analogs; frozen dairy desserts and mixes; desserts and mousses; confections and frostings; snack foods; coatings and fillings; salad dressings; soups and soup mixes; and sauces.

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[13] American Dairy Products Institute, GRN000037 (regarding whey protein isolate and dairy product solids), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm266140.pdf (last accessed on November 28, 2017), and April 21, 2000 FDA Response to GRN000037, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154133.htm (last accessed on November 28, 2017).

[14] Glanbia Ingredients, GRN000052 (regarding whey mineral concentrate), available at https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=52 (last accessed on November 28, 2017), and January 30, 2991 FDA Response to GRN000052, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm153729.htm (last accessed on November 28, 2017).

[15] Snow Brand Milk Products, GRN000196 (regarding bovine milk basic protein fraction), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm263904.pdf (last accessed on November 28, 2017), and September 1, 2006 FDA Response to GRN000196, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154673.htm (last accessed on November 28, 2017).

[16] American Dairy Products Institute, GRN000504 (regarding whey proteins), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm400536.pdf (last accessed on November 28, 2017), and November 21, 2014 FDA Response to GRN000504, available at https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm427497.htm (last accessed on November 28, 2017).

Finally, in GRN000633, FDA had no questions regarding the GRAS determination related to "whey protein" consisting of concentrated milk protein with a ratio of ≥60 whey to 40 casein for use as an emulsifier, flavoring agent, formulation aid, humectant, stabilizer, thickener, texturizer, and protein source in meal replacements and meal supplements; powdered nutritional beverages; nutritional bars; acidified sports beverages; milk products; yogurt and fermented milk products; non-standardized cheese products; spreads, dips and cream substitutes; frozen dairy desserts and mixes; desserts and mousses; confections; snack foods; coatings and fillings; salad dressings; soups, soup mixes, and sauces.[17]

The GRAS Affirmations and Notices above exhibit FDA's confidence in the safety of these milk-derived ingredients. Similar to the milk-derived ingredients above, alpha-lactalbumin is produced using physical processes that do not present any safety concerns that have not already been addressed in the existing, favorably-reviewed GRAS Affirmations and Notices discussed above.

A. Safety Overview

Due to the substantial similarities between alpha-lactalbumin and traditional whey protein, as well as the substantial similarities between these products and the concentrated milk proteins that are the subject of GRN000504, the safety discussion related to the latter group of products is directly applicable to establishing the safety and GRAS status of alpha-lactalbumin. We incorporate the safety overview provided in GRN000504 by reference and highlight the relevance of those safety data to our assessment of alpha-lactalbumin below.

1. Human Consumption of Milk Protein

The raw material used in the manufacture of alpha-lactalbumin is milk or skim milk. Milk and products derived from milk, 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.

2. Purification of Alpha-Lactalbumin

Alpha-lactalbumin is manufactured using safe and well-characterized physical separation techniques that are analogous to the processes employed in the manufacture of the whey protein concentrate and whey protein isolate products described above. Such physical separation processes do not cause substantive alterations to the chemical character and safety-related properties of the constituents. The food additives that may be utilized in the manufacturing process for alpha-lactalbumin are all either approved food additives or GRAS food ingredients for these applications and are used in accordance with food GMPs. The manufacturing process does not generate, concentrate, or introduce any potential toxicants. As a result, the alpha-lactalbumin is as safe as milk itself.

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[17] Leprino Foods, GRN000633 (regarding concentrated milk proteins), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505250.pdf (last accessed on November 28, 2017), and September 21, 2016 FDA Response to GRN000633, available at https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm528187.htm (last accessed on November 28, 2017).

3. Safety Studies on Alpha-Lactalbumin

Given the long history of human consumption, milk and milk proteins are of little toxicological concern to humans or animals. With the exception of particularly sensitive populations – namely milk-allergic and lactose-intolerant individuals, whom we address immediately below – we are not aware of adverse effects associated with consumption of alpha-lactalbumin. In addition, a literature search does not yield any reported adverse effects.

4. Allergenicity of Milk Protein

An allergy to milk is among the eight most common food allergies.[18] Because the substances are chemically identical, milk and isolated milk proteins will produce a milk protein allergy when consumed. All concentrated milk protein ingredients, including alpha-lactalbumin, will clearly indicate that the product is derived from milk protein and will inform those consumers who are allergic to milk and satisfy food allergen labeling requirements.

For any food containing alpha-lactalbumin, the label will bear a statement indicating that the product has been derived from a milk source to satisfy allergen labeling requirements.

5. Lactose Intolerance

Lactose intolerance is the inability or insufficient ability to digest lactose, a sugar found in milk and milk products. Lactose intolerance is caused by a deficiency of the enzyme lactase, which is produced by the cells lining the small intestine. Lactase breaks down lactose into two simpler forms of sugar called glucose and galactose, which are then absorbed into the bloodstream. People with lactose intolerance may feel uncomfortable 30 minutes to 2 hours after consuming milk and milk products. Symptoms range from mild to severe based on the amount of lactose consumed and the amount a person can tolerate. Common symptoms include abdominal pain, abdominal bloating, gas, diarrhea, and nausea.[19]

Research indicates that most people with lactose intolerance are able to consume the amount of lactose in up to two cups of milk a day if taken with meals, one at breakfast and the other at dinner. Other dairy foods, such as aged cheese and yogurts are also well-tolerated because lactose is converted to lactic acid by select microorganisms during the making of the products.[20]

The percentage of lactose is inversely related to the protein content of the concentrated milk protein. The percentage of lactose in alpha-lactalbumin products is <0.2%. This level is

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[18] "Eight major foods or food groups – milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans– account for 90% of food allergies." Pub. L. 108-282, title II § 202(1)(2)(A) (Aug. 2, 2004).

[19] Lactose Intolerance, National Digestive Diseases Information Clearinghouse (NDDIC), available at http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/ (last accessed on November 28, 2017).

[20] National Dairy Council, Handbook of Dairy Foods and Nutrition 6 (3rd ed. 2006).

order of magnitude lower than the level of lactose in Nonfat Dry Milk, which is around 49.0-52.3%.[21] Therefore, we do not anticipate any unique impact on lactose sensitive populations.[22]

B. Summary of Basis for GRAS Determination

Agropur has determined that alpha-lactalbumin is Generally Recognized as Safe (GRAS) based on the following:

- The fact that alpha-lactalbumin is manufactured under current good manufacturing practices (cGMP) for food (21 C.F.R. Part 110) and meets appropriate food grade specifications;
- That potential contaminants, such as pesticides and heavy metals, are either absent (not detected) or below toxicological and regulatory limits;
- The digestibility and nutritional quality of alpha-lactalbumin;
- The intended uses and the estimated consumption of alpha-lactalbumin;
- The proper labeling of the products;
- Supportive evidence from the long history of safe use of milk and milk protein as food; and
- Supportive evidence from the successful GRAS Notice for concentrated milk proteins, GRN000504.

VII. List of supporting data and information in your GRAS Notice (21 C.F.R. § 170.255)

1. American Dairy Products Institute, GRN000037 (regarding whey protein isolate and dairy product solids), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm266140.pdf (last accessed on November 28, 2017), and April 21, 2000 FDA Response to GRN000037, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154133.htm (last accessed on November 28, 2017).
2. American Dairy Products Institute, GRN000504 (regarding whey proteins), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm400536.pdf (last accessed on November 28, 2017), and November 21, 2014 FDA Response to GRN000504, available at https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm427497.htm (last accessed on November 28, 2017).

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[21] The Really Big List of Lactose Percentages, available at http://www.stevecarper.com/li/list_of_lactose_percentages.htm (last accessed on November 28, 2017).

[22] Additional information on lactose intolerance can be found in the scientific status report from the National Dairy Council, Science Summary: Dairy & Lactose Intolerance (February 23, 2016), available at https://www.nationaldairycouncil.org/content/2015/science-summary-dairy-and-lactose-intolerance (last accessed on November 28, 2017).

3. Bonlac Foods Limited, GRN000011 (regarding Calcium casein peptone-calcium phosphate), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm264465.pdf (last accessed on November 28, 2017), and January 29, 1999 FDA Response to GRN000011, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154906.htm (last accessed on November 28, 2017).
4. Bos C, Gaudichon C, Tome D. Nutritional and physiological criteria in the assessment of milk protein quality for humans. J Am Coll Nutr 2000;19(suppl):191S–205S.
5. Bos C, Mahe S, Gaudichon C, et al. Assessment of net postprandial protein utilization of 15N-labelled milk nitrogen in human subjects. Br J Nutr 1999;81:221–6.
6. Bos C, Metges CC, Gaudichon C, et al. Postprandial kinetics of dietary amino acids are the main determinant of their metabolism after soy or milk protein ingestion in humans. J Nutr 2003;133:1308–15.
7. Cook BB, Morgan AF, Singer B, Parker J. The effect of heat treatment on the nutritive value of milk proteins. II. Rat growth studies with casein and lactalbumin and their lactose derivatives. J Nutr 1951;44:63–81.
8. Dietary protein quality evaluation in human nutrition: Report of an FAO Expert Consultation, FAO Food and Nutrition Paper 92 (FAO, 2013).
9. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Total Water and Macronutrients. Food and Nutrition Board, Institute of Medicine, National Academies, available at https://www.ncbi.nlm.nih.gov/books/NBK56068/table/summarytables.t4/?report=objectonly (last accessed on November 28, 2017).
10. FDA, Grade "A" Pasteurized Milk Ordinance (2013 Revision), at Appendix N ("Drug Residue Testing and Farm Surveillance – Industry Responsibilities – Monitoring and Surveillance").
11. Gaudichon C, Mahe S, Benamouzig R, et al. Net postprandial utilization of [15N]-labeled milk protein nitrogen is influenced by diet composition in humans. J Nutr 1999;129:890–5.
12. Gausseres N, Mahe S, Benamouzig R, et al. [15N]-labeled pea flour protein nitrogen exhibits good ileal digestibility and postprandial retention in humans. J Nutr 1997;127:1160–5.
13. Gilani GS, Sepehr E. Protein digestibility and quality in products containing antinutritional factors are adversely affected by old age in rats. J Nutr 2003;133:220–5.
14. Glanbia Ingredients, GRN000052 (regarding whey mineral concentrate), available at https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=52 (last accessed on November 28, 2017), and January 30, 1991 FDA Response to GRN000052, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm153729.htm (last accessed on November 28, 2017).

15. Institute of Food Technologists, Food Chemistry Experiments, IFT Experiments in Food Science Series, at page 3-1, available at http://www.ift.org/~/media/Knowledge%20Center/Learn%20Food%20Science/Experiments/TeacherGuidePROTEINS.pdf (last accessed on November 28, 2017).

16. Joint FFAO/WHO Food Standards Programme Codex Committee on Nutrition and Foods for Special Dietary Uses, Thirty-Eighth Session (Hamburg, Germany, 5 – 9 December 2016), Review Of The Standard For Follow-Up Formula (Codex Stan 156-1987), Physical Working Group Report, at http://www.fao.org/fao-who-codexalimentarius/sh-proxy/es/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-720-38%252FCRDs%252FCRD_13.pdf (last accessed November 28, 2017).

17. Lactose Intolerance, National Digestive Diseases Information Clearinghouse (NDDIC), available at http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/ (last accessed on November 28, 2017).

18. Leprino Foods Company, GRN000633 regarding concentrated milk proteins, available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505250.pdf (last accessed November 28, 2017), citing DH Business Consulting and Associates, Micellar casein ingredients business & market analysis (2013).

19. Leprino Foods, GRN000633 (regarding concentrated milk proteins), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm505250.pdf (last accessed on November 28, 2017), and September 21, 2016 FDA Response to GRN000633, available at https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm528187.htm (last accessed on November 28, 2017).

20. Morens C, Bos C, Pueyo ME, et al. Increasing habitual protein intake accentuates differences in postprandial dietary nitrogen utilization between protein sources in humans. J Nutr 2003;133:2733–40.

21. National Dairy Council, Handbook of Dairy Foods and Nutrition 6 (3rd ed. 2006).

22. National Dairy Council, Science Summary: Dairy & Lactose Intolerance (February 23, 2016), available at https://www.nationaldairycouncil.org/content/2015/science-summary-dairy-and-lactose-intolerance (last accessed on November 28, 2017).

23. Pub. L. 108-282, title II § 202(1)(2)(A) (Aug. 2, 2004).

24. Rutherford et al., Protein digestibility-corrected amino acid scores and digestible indispensable amino acid scores differentially describe protein quality in growing male rats. J Nutr. 2015 Feb;145(2):372-9. 2014 Nov 26, summary available at https://www.ncbi.nlm.nih.gov/pubmed/25644361 (last accessed November 28, 2017).

25. Rutherfurd SM, Moughan PJ. The digestible amino acid composition of several milk proteins: application of a new bioassay. J Dairy Sci 1998; 81:909–17.

26. Schaafsma G. The Protein Digestibility-Corrected Amino Acid Score. J Nutr 2000; 130:1865S-1867S (internal citations omitted).

27. Snow Brand Milk Products, GRN000196 (regarding bovine milk basic protein fraction), available at https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm263904.pdf (last accessed November 28, 2017), and September 1, 2006 FDA Response to GRN000196, available at http://www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm154673.htm (last accessed on November 28, 2017).

28. The Really Big List of Lactose Percentages, available at http://www.stevecarper.com/li/list_of_lactose_percentages.htm (last accessed on November 28, 2017).

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Based on the documentation provided in this GRAS Notice, and as discussed above, Agropur Inc. has concluded that alpha-lactalbumin is GRAS based on scientific procedures for use in nutritional products and dairy-based products.