JHeimbach LLC

November 16, 2020

Susan J. Carlson, Ph.D., Director
Office of Food Additive Safety (HFS-200),
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Dr., College Park, MD 20740

Dear Dr. Carlson:

Pursuant to 21 CFR Part 170, Subpart E, ByHeart, Inc., through me as its agent, hereby provides notice of a claim that the addition of dry whole milk to nonexempt infant formula intended for consumption by healthy term infants from the first day of life is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because ByHeart, Inc., has determined that the intended use is generally recognized as safe (GRAS) based on scientific procedures.

A CD is enclosed containing Form 3667, the GRAS monograph, and the signatures of members of the GRAS panel in a zip directory produced through COSM.

If you have any questions regarding this notification, please feel free to contact me at 202-320-3063 or jh@jheimbach.com.

Sincerely,

[redacted]

James T. Heimbach, Ph.D., F.A.C.N.
President

Encl.

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Generally Recognized as Safe (GRAS) Determination for the Intended Use of Dry Whole Milk in Nonexempt Infant Formula

Prepared for:
ByHeart, Inc.
New York, NY

Prepared by:
JHeimbach LLC
Port Royal Virginia

November, 2020

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Part 1: Signed Statements and Certification

1.1. GRAS Notice Submission

ByHeart, Inc., submits this GRAS notification through its agent James T. Heimbach, president of JHeimbach LLC, in accordance with the requirements of 21 CFR Part 170, Subpart E.

1.2. Name and Address of Notifier

ByHeart, Inc.
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14th Floor
New York NY 10022

Notifier Contact
Gyan Rai, Ph.D.
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Agent Contact
James T. Heimbach, Ph.D., F.A.C.N.
President
JHeimbach LLC
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1.3. Name of Notified Substance

The subject of this Generally Recognized as Safe (GRAS) notice is dry whole milk as defined in 21 CFR §131.147, produced under current Good Manufacturing Practice (cGMP).

1.4. Intended Conditions of Use

As described in Section 3.1, the intended use of dry whole milk is as a component of non-exempt infant formula intended for consumption by healthy term infants from the first day of life. The addition level, allowing for manufacturing variability under cGMP, will not exceed 16% (w/w) of the powdered infant formula.

1.5. Statutory Basis for GRAS Status

ByHeart's GRAS determination for the intended use of dry whole milk in infant formula is based on scientific procedures in accordance with 21 CFR §170.30(b).

Determination of the safety and GRAS status of the intended use of dry whole milk has been made through the deliberations of a GRAS Panel consisting of Ronald Kleinman, M.D., Berthold V. Koletzko, M.D., Ph.D., and Robert J. Nicolosi, Ph.D. These individuals are qualified by scientific training and experience to evaluate the safety of food ingredients intended for addition

to infant formula. They independently critically reviewed and evaluated the publicly available information and the potential human exposure to dry whole milk anticipated to result from its intended use, and individually and collectively determined that no evidence exists in the available information on whole milk that demonstrates, or suggests reasonable grounds to suspect, a hazard to infants or toddlers under the intended conditions of use of dry whole milk.

It is the GRAS Panel's opinion that other qualified scientists reviewing the same publicly available information would reach a similar conclusion regarding the safety of the substance under its intended conditions of use. Therefore, the intended use of dry whole milk in non-exempt infant formula intended for consumption by healthy term infants from the first day of life is GRAS by scientific procedures.

1.6. Premarket Exempt Status

The intended use of dry whole milk is not subject to the premarket approval requirements of the Federal Food, Drug and Cosmetic Act based on ByHeart's determination that it is GRAS.

1.7. Data Availability

The data and information that serve as the basis for the conclusion that dry whole milk is GRAS for its intended use will be made available to the FDA upon request. At FDA's option, a complete copy of the information will be sent to FDA in either paper or electronic format, or the information will be available for review at the home office of JHeimbach LLC, located at 923 Water Street, Port Royal VA 22535, during normal business hours.

1.8. Freedom of Information Act Statement

None of the information in this GRAS notice is exempt from disclosure under the Freedom of Information Act, USC 552.

1.9. Certification

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 me and pertinent to the evaluation of the safety and GRAS status of the intended use of dry whole milk.

1.10. FSIS Statement

Not applicable.

1.11. Name, Position, and Signature of Notifier

James T. Heimbach, Ph.D., F.A.C.N.
President
JHeimbach LLC
Agent to ByHeart, Inc.

Part 2: Identity, Methods of Manufacture, Specifications, and Physical and Technical Effects

2.1. Name of the GRAS Substance

The notified substance is dry whole milk, which is defined in 21 CFR §131.147 as "the product obtained by removal of water only from pasteurized milk, as defined in §131.110(a), which may have been homogenized. Alternatively, dry whole milk may be obtained by blending fluid, condensed, or dried nonfat milk with liquid or dried cream or with fluid, condensed, or dried milk, as appropriate, provided the resulting dry whole milk is equivalent in composition to that obtained by the method described in the first sentence of this paragraph. It contains the lactose, milk proteins, milkfat, and milk minerals in the same relative proportions as the milk from which it was made. It contains not less than 26 percent but less than 40 percent by weight of milkfat on an as is basis. It contains not more than 5 percent by weight of moisture on a milk solids not fat basis." This section further notes that addition of vitamins A and D is optional, along with carriers for these vitamins, emulsifiers, stabilizers, anticaking agents, and antioxidants.

The dry whole milk that is the subject of this GRAS notice does not contain added vitamins A or D or any of the other optional ingredients identified above.

2.2. Source, Description, Manufacture, and Specifications

2.2.1. Source and Description

ByHeart's dry whole milk is sourced from dairy cows. The composition of dry whole milk, as described in the U.S. Department of Agriculture's Nutrient Database for Standard Reference (USDA 2020) is shown in Table 1. As with any biological substance, there is some natural variability in the values reported, which is not reflected in the USDA tables.

Table 1. Composition in 100 g Dry Whole Milk Without Added Vitamin D (USDA 2020).

Parameter	Level	Unit
Proximates		
Water	2.47	g
Energy	496	kcal
Energy	2075	kJ
Protein	26.32	g
Total lipid (fat)	26.71	g
Ash	6.08	g
Carbohydrate, by difference	38.42	g
Fiber, total dietary	0	g
Sugars, total including NLEA	38.42	g
Minerals		
Calcium, Ca	912	mg
Iron, Fe	0.47	mg
Magnesium, Mg	85	mg
Phosphorus, P	776	mg
Potassium, K	1330	mg
Sodium, Na	371	mg
Zinc, Zn	3.34	mg
Copper, Cu	0.08	mg
Manganese, Mn	0.04	mg
Selenium, Se	16.3	µg

Vitamins		
Vitamin C, total ascorbic acid	8.6	mg
Thiamin	0.283	mg
Riboflavin	1.205	mg
Niacin	0.646	mg
Pantothenic acid	2.271	mg
Vitamin B-6	0.302	mg
Folate, total	37	µg
Folic acid	0	µg
Folate, food	37	µg
Folate, DFE	37	µg
Choline, total	117.4	mg
Vitamin B-12	3.25	µg
Vitamin B-12, added	0	µg
Vitamin A, RAE	258	µg
Retinol	253	µg
Carotene, beta	55	µg
Carotene, alpha	0	µg
Cryptoxanthin, beta	0	µg
Vitamin A, IU	934	IU
Lycopene	0	µg
Lutein + zeaxanthin	0	µg
Vitamin E (alpha-tocopherol)	0.58	mg
Vitamin E, added	0	mg
Vitamin D (D2 + D3), International Units	20	IU
Vitamin D (D2 + D3)	0.5	µg
Vitamin D3 (cholecalciferol)	0.5	µg
Vitamin K (phylloquinone)	2.2	µg
Fatty Acids & Cholesterol		
Fatty acids, total saturated	16.742	g
4:00	0.866	g
6:00	0.24	g
8:00	0.269	g
10:00	0.596	g
12:00	0.614	g
14:00	2.82	g
16:00	7.522	g
18:00	2.853	g
Fatty acids, total monounsaturated	7.924	g
16:01	1.196	g
18:01	6.192	g
20:01	0	g
22:01	0	g
Fatty acids, total polyunsaturated	0.665	g
18:02	0.46	g

18:03	0.204	g
18:04	0	g
20:04	0	g
20:5 n-3 (EPA)	0	g
22:5 n-3 (DPA)	0	g
22:6 n-3 (DHA)	0	g
Cholesterol	97	mg
Amino Acids		
Tryptophan	0.371	g
Threonine	1.188	g
Isoleucine	1.592	g
Leucine	2.578	g
Lysine	2.087	g
Methionine	0.66	g
Cystine	0.243	g
Phenylalanine	1.271	g
Tyrosine	1.271	g
Valine	1.762	g
Arginine	0.953	g
Histidine	0.714	g
Alanine	0.908	g
Aspartic acid	1.997	g
Glutamic acid	5.512	g
Glycine	0.557	g
Proline	2.549	g
Serine	1.432	g
Other		
Alcohol, ethyl	0	g
Caffeine	0	mg
Theobromine	0	mg

2.2.2. Manufacture

ByHeart's dry whole milk is produced using standard dairy processing techniques involving purely mechanical procedures as shown in Figure 1. No component of whole milk is concentrated to greater than naturally occurring levels.

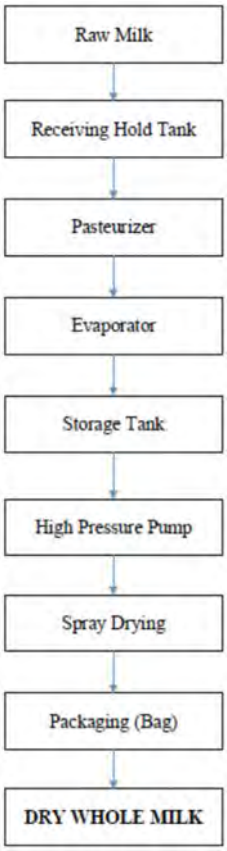


Figure 1. Process Flow Diagram of ByHeart's Dry Whole Milk.

2.2.3. Specifications

ByHeart has established food-grade specifications for dry whole milk to assure purity. Table 2 shows the results of analyses of three non-consecutive lots of product to determine compliance with these specifications. As is shown, all samples were in full compliance, indicating that the production process is in control and results in product that consistently meets food-grade specifications.

Table 2. Analyses of Three Non-Consecutive Lots of Dry Whole Milk Against Specifications.

Parameter	Specification	Lot Tested			Method (Eurofins)
		MO19-0019	MO20-0014	MO20-0015	
Moisture (%)	NMT[1] 5.0	2.30	3.13	3.07	M100_T100 (AOAC 925.09 / 926.08)
Protein (%)	NLT[2] 18.7	25.3	25.0	25.0	DGEN_S (AOAC 968.06 / 992.15)
Fat (%)	NLT 26	32.9	32.0	31.8	FAT_BH_S (AOAC 989.05/932.05/986.25/945.48B)
Titratable acidity (%)	NMT 15	<15	<15	<15	QA-PL-10.000 (USDA 918RL)
Peroxide value (meq/kg fat)	NMT 5	1.0	2.9	2.1	AOAC 965.33
Cholesterol (mg/100 g)	Typical concentration	107	99.0	99.2	CHOK-S (AOAC 994.10)
Ash (%)	Typical concentration	5.2%	5.2%	5.2%	ASHM_S (AOAC 923.03)
Vitamin A (IU/100 g)	Typical concentration	804	943	914	VALC_S (AOAC 992.04/992.06/2001.13)
Vitamin D3 (IU/100 g)	Typical concentration	<4	<4	<4	VDMS_S (AOAC 2011.11)
Iron (mg/g)	Typical concentration	0.003	0.003	0.003	ICP_S (AOAC 984.27 / 985.01/2011.14)
Iodide (µg/g)	Typical concentration	3.32	1.11	1.11	IODICPMS_S (AOAC 2212.15)
Sodium (mg/g)	Typical concentration	3.01	2.94	2.92	ICP_S (AOAC 984.27 / 985.01/2011.14)
Potassium (mg/g)	Typical concentration	11.06	10.81	10.75	ICP_S (AOAC 984.27 / 985.01/2011.14)
Chloride (mg/g)	Typical concentration	7.97	7.19	7.15	CL_SALT_S (AOAC 963.05/971.27/986.26)
Selenium (µg/g)	Typical concentration	0.120	0.703	0.715	SEIF_S (AOAC 2011.19)
Heavy metals					
Arsenic (µg/kg)	NMT 500	<10	<10	<10	ICP-MS (AOAC 2011.19 / 993.14)
Cadmium (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Lead (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Mercury (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Microbiological					
Aerobic Plate Count (cfu[3]/g)	NMT 10,000	160	60	50	APC (AOAC 966.23)
Coliforms (cfu/g)	NMT 10	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
Mold (cfu/g)	NMT 50	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
Yeast (cfu/g)	NMT 50	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
B. cereus (cfu/g)	NMT 100	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
Enterobacteri-aceae (cfu/g)	NMT 10	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
S. aureus	NMT 10	<10	<10	<10	YN_SPRD (AOAC, FDA BAM)
Listeria spp. (in 25 g)	Negative	Not detected	Not detected	Not detected	YN_SPRD (AOAC, FDA BAM)
Salmonella LAMP detection (in 25 g)	Negative	Not detected	Not detected	Not detected	SALLAMP (AOAC 091501)
Cronobacter species D (in 10 g)	Negative	Not detected	Not detected	Not detected	ICO_EML_LC (AOAC, FDA BAM)

1. NMT = not more than
2. NLT = not less than
3. cfu = colony-forming units

2.3. Stability

One lot of dry whole milk was stored for ten months at a temperature ranging from 10-30ºC and relative humidity <70% and two additional lots were stored for four months under the same conditions. The results of the 10-month study are shown in Table 3 and those of the 4-month studies in Table 4. The data from all studies indicate that no significant degradation in the quality of the dry milk occurs over the time periods studied.

Table 3. Stability of Dry Whole Milk over 10 Months.

Lot MO19-0019											
Parameter	**Time 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**
Moisture (%)	2.30	2.51	2.58	2.56	2.18	1.92	3.06	2.61	2.78	3.20	3.48
Free Fat (%)	5.3	3.6	4.6	3.6	6.3	4.9	4.7	3.3	2.4	1.9	3.3
Free Fatty Acids (%)	0.03	0.09	---[1]	0.09	0.08	0.09	0.07	0.06	0.11	0.08	0.14
Hexanal (mg/kg)	<1.00	<1.00	1.07	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Peroxide (% mEq/kg)	2.1	1	1.5	1.1	1.8	1.9	2.1	1.8	2.0	1.5	1.4
Yeast (cfu[2]/g)	---	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Mold (cfu/g)	---	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Aerobic plate count (cfu/g)	---	210	430	390	240	300	200	430	150	150	490
Color (L value))	92.48	92.32	92.27	92.24	92.45	92.53	92.62	92.27	92.28	---	92.13
Color (A value)	-1.99	-2.03	-2.15	-2.26	-2.07	-2.34	-2.25	-2.38	-2.37	---	-2.40
Color (B value)	21.19	21.67	22.06	22.01	20.63	21.21	20.88	22.06	22.00	---	22.19
Nitrogen solubility (%)	77	---	---	---	---	---	---	---	---	73.2	---

1. Not tested.
2. cfu = colony-forming units

Table 4. Stability of Dry Whole Milk over 4 Months.

Parameter	**MO20-0014**					**MO20-0015**				
	Time 0	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Time 0**	**Month 1**	**Month 2**	**Month 3**	**Month 4**
Moisture (%)	3.13	2.48	2.98	3.40	3.58	3.07	2.39	2.91	3.23	3.41
Free Fat (%)	1.6	1.1	1.5	1.0	1.6	1.7	1.6	1.0	1.3	1.5
Free Fatty Acids (%)	0.10	0.07	0.07	0.06	0.14	0.06	0.07	0.07	0.06	0.13
Hexanal (mg/kg)	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Peroxide (% mEq/kg)	3.5	2.9	1.7	1.5	1.9	1.0	2.1	2.6	1.4	1.5
Yeast (cfu[2]/g)	---[1]	<10	<10	<10	<10	---	<10	<10	<10	<10
Mold (cfu/g)	---	<10	<10	<10	<10	---	<10	<10	10	<10
Aerobic plate count (cfu/g)	---	80	70	<10	80	---	60	110	<10	10
Color (L value))	91.68	91.47	91.76	---	91.94	91.70	91.70	91.43	---	91.60
Color (A value)	-1.39	-1.33	-1.46	---	-1.71	-1.4	-1.4	-1.45	---	-1.72
Color (B value)	22.94	23.51	22.79	---	22.54	22.99	23.01	23.56	---	23.38
Nitrogen solubility (%)	78.9	64.9	---	---	---	79.7	---	---	---	---

1. Not tested.
2. cfu = colony-forming units

2.4. Technical Effect

The intended technical effect of the addition of dry whole milk to nonexempt infant formula is as a source of protein. It is not intended to serve any function other than nutrition.

Part 3: Dietary Exposure

3.1. Intended Conditions of Use

21 CFR §107.100 provides nutrient specifications for milk-based infant formula per 100 kcal formula as prepared. These specifications are summarized in Table 5.

Table 5. Nutrient Specifications for Milk-Based Infant Formula (from 21 CFR §107.100).

Nutrient	Unit of Measurement	Minimum Level per 100 kcal	Maximum Level per 100 kcal
Protein	g	1.8	4.5
Fat	g	3.3	6.0
	% kcal	30	54
Linoleic acid	mg	300	
	% kcal	2.7	
Vitamin A	IU	250	750
Vitamin D	IU	40	100
Vitamin E	IU	0.7	
Vitamin K	µg	4	
Thiamine (Vitamin B_1)	µg	40	
Riboflavin (Vitamin B_2)	µg	60	
Vitamin B_6	µg	35	
Vitamin B_{12}	µg	0.15	
Niacin	µg	250	
Folic acid (Folacin)	µg	4	
Pantothenic acid	µg	300	
Vitamin C (Ascorbic acid)	mg	8	
Calcium	mg	60	
Phosphorus	mg	30	
Magnesium	mg	6	
Iron	mg	0.15	3.0
Zinc	mg	0.5	
Manganese	µg	5	
Copper	µg	60	
Iodine	µg	5	75
Selenium	µg	2	7
Sodium	mg	20	60
Potassium	mg	80	200
Chloride	mg	55	150

Dry whole milk powder will be added to powdered infant formula at a level not exceeding 16 g/100 g powder. The infant formula to be manufactured by ByHeart will have a hydration rate of 12.5 g powder/100 ml formula ready to consume; this level is equivalent to 2.0 g dry whole milk/100 ml formula ready to consume. The function of the addition of dry milk powder is to provide nutrients more closely resembling those found in breast milk.

3.2. Estimated Daily Exposure

Assuming an average formula intake of 800 ml/day, an infant will consume 16.0 g dry whole milk powder per day. (This represents the solids content of approximately 120 ml whole milk.)

According to tables of daily energy intake by formula-fed infants provided by Fomon (1993), the subpopulation of infants with the highest energy intake per kg body weight is boys age 14–27 days. The 90th percentile energy intake by this group is 141.3 kcal/kg bw/day. Among girls, the highest energy intake is found in the same age group, 14–27 days, and is nearly as high as boys:

138.9 kcal/kg bw/day[1]. Most standard formulas contain 67 kcal/100 ml when ready to consume. Therefore, to obtain 141.3 kcal energy/kg bw, an infant boy must consume 209.0 ml formula/kg bw. To reach her 90th percentile of energy consumption, 138.9 kcal/kg bw/day, an infant girl must consume 205.5 ml formula/kg bw. The 90th percentile of formula intake for the two sexes combined is about 207 ml/kg bw/day.

Since dry milk powder is to be added at a maximum level of 2.0 g dry whole milk/100 ml formula ready to consume, the 90th percentile daily intake of dry whole milk is estimated to be [2.0 g dry whole milk/100 ml x 207 ml/kg bw/day] = 4.14 g dry whole milk/kg bw/day.

As the infant grows, formula intake increases, but more slowly than weight gain, so that consumption assessed as ml formula per kg body weight is lower for infants older than 27 days. As a result, intake of dry whole milk per kg body weight decreases as the infant grows older and larger.

3.2.1. Phospholipids and Other Lipids

The amounts of phospholipids provided by the intended use of dry whole milk powder, resulting in 2.0 g dry whole milk/100 ml formula, as compared to levels in human breast milk, are shown in Table 6. As has been previously noted, the composition of the whole milk has not been altered in any way; the phospholipids are present at their naturally occurring levels. The amounts listed in Table 6 are total phospholipid composition that may originate from intact or disrupted milk fat globules.

As is evident from Table 6, the levels of phospholipids provided by dry whole milk do not differ remarkably from those provided by the human milk consumed by breastfed infants. When infant formula is based on nonfat milk, some of the native phospholipids are removed during the defatting steps and so "Breastfed infants have a higher intake of [these phospholipids] than their formula-fed counterparts because, traditionally, the [phospholipid] fraction is discarded with the milk fat when this is replaced by vegetable oils as the fat source in infant formulas" (Timby et al. 2017). Phospholipids are permitted to be added to infant formulas up to a maximum concentration of 300 mg/100 kcal (equivalent to about 2 g/L) and are regarded as safe (Koletzko et al. 2005). Phospholipid ingredients such as lecithin used in other commercial formulas today provide partial replacement of these phospholipids (Scholfield 1981). As is evident in Table 6, the phospholipid composition of ByHeart's formula is not remarkably different from currently marketed infant formulas with and without added MFGM (Fong et al 2013), and the values are within the ranges observed in human milk (Ma et al 2017).

[1] These estimates are corroborated by data from the 2008 Feeding Infants and Toddlers Study (FITS; Butte et al. 2010), which reported the 90th percentile energy intake for infants aged birth to 5 months as 779 kcal. Although body weights of the FITS participants on the days diets were assessed were not available, infant growth charts issued by the Centers for Disease Control and Prevention indicate that the median body weights for the two sexes combined at birth and at 5 months are about 3.4 and 7.4 kg, respectively. A reasonable estimate of the median body weight of infants aged birth to 5 months is the average of these two body weights, or 5.4 kg. The 90th percentile energy intake of 779 kcal thus represents about 144 kcal/kg, very close to the estimates in Fomon (1993).

Table 6. Phospholipids Provided by Dry Whole Milk vs. Breast Milk and Current US Commercial Formula.

Phospholipid	% in Whole Milk Powder[1]	mg/100 ml in ByHeart formula[2]	mg/100 ml in breast milk	mg/100 ml in commercial product #1 without added MFGM	mg/100 ml in commercial product #2 with added MFGM
Total phospholipid	0.286	13.6	17.0 ± 8.0	53.7	86.2
Phosphatidylcholine	0.067	3.3	2.6 ± 1.7	18.2	26.0
Phosphatidylethanolamine	0.0636	0.3	4.6 ± 2.3	11.7	16.9
Phosphatidylinositol	0.037	1.7	0.7 ± 0.5	7.8	13.0
Phosphatidylserine	0.033	1.7	1.7 ± 1.0	2.6	6.5
Sphingomyelin	0.057	5.0	6.5 ± 3.8	2.6	13.0

1. Analytical data from independent testing laboratory.
2. Calculated from analytical data for 16% addition rate.

Certain other lipids present in human and bovine milk are listed in Table 7. They are largely removed during defatting of milk but are still present in small amounts in nonfat milk. As shown in Table 7, their contribution to By Heart's infant formula from the whole milk is small and their levels are within the ranges of both human milk (McGuire et al. 1997; Floris et al. 2020) and commercial infant formula.

Table 7. Other Lipids Provided by Dry Whole Milk vs. Breast Milk and Current US Commercial Formula.

Other Lipids	% in Whole Milk Powder[1]	mg/100 ml in ByHeart formula[2]	mg/100 ml in breast milk	mg/100 ml in commercial product #1 without added MFGM	mg/100 ml in Commercial product #2 with added MFGM
Conjugated linoleic acid (mg/g fat)	9.9 - 17.3	2.4*	3.64 ± 0.93	1.7	2.1
Cholesterol (mg/g fat)	3.12 - 3.25	0.90	2.0 – 5.64	0.62	1.6
trans-fatty acids (% total FA)	4.6 - 8.5	1.03	1.28 ± 0.27	0.54	1.14

1. Analytical data from independent testing laboratory.
2. Calculated from analytical data for 16% addition rate.

Although several infant formula feeding studies (e.g., Billeaud et al. 2014) that have been conducted with MFGM added to infant formula, showed equivalent growth in comparison to infant formula without MFGM, these conditions do not apply in this situation as the contribution of milk fat and its lipid components are insignificant in relation to the vegetable fat or those used in MFGM-supplemented infant formulas. Furthermore, the amounts of phospholipids in ByHeart formula is similar to the range observed in human milk and that in currently sold commercial infant formula without added MFGM, and is substantially lower than those in MFGM-supplemented infant formulas.

3.2.2. Nutrients with Maximum Allowable Levels

The nutrient specifications for milk-based infant formula listed in 21 CFR §107.100 include ten nutrients for which maximum allowable levels are specified—protein, fat, vitamins A and D, iron, iodine, selenium, sodium, potassium, and chloride. Table 8 shows the amount of these nutrients provided by dry whole milk added at the maximum intended level of 16%. These data show that the intended addition of dry whole milk does not cause the allowable levels of any of these nutrients to be exceeded.

Table 8. Nutrients Provided by Dry Whole Milk and Maximum Allowable Levels.

Nutrient	Unit of Measurement	Level Provided by Dry Whole Milk per 100 kcal	Maximum Allowable Level per 100 kcal
Protein	g	0.76	4.5
Fat	g	0.97	6.0
	% kcal	8.8	54
Vitamin A	IU	27	750
Vitamin D	IU	0.12	100
Iron	mg	0.009	3.0
Iodine	µg	5.6	75
Selenium	µg	1.5	7
Sodium	mg	8.9	60
Potassium	mg	33	200
Chloride	mg	22	150

Part 4: Self-limiting Levels of Use

There is no physical limit to the concentration of milk in infant formula; infants have been fed 100% cow's milk in the past. However, an excessive amount of milk in the infant formula would lead to nutrient imbalances, which places a limit on the addition level.

Part 5: Experience Based on Common Use in Food

The conclusion that the intended use of dry whole milk is GRAS is based on scientific procedures rather than experience based on common use in food prior to 1958.

Part 6: Narrative

6.1. Regulatory Status of Whole Milk and Dry Whole Milk

While bovine whole milk is not listed as a GRAS substance in 21 CFR §184, it is appropriate to note that the long history of use of whole milk (in liquid or dry form) as both a stand-alone product and an ingredient in a wide variety of products—including infant formula—suggests that it has been informally recognized as GRAS as an ingredient in conventional foods. Regarding this point, 21 CFR §182.1 notes that:

> "It is impracticable to list all substances that are generally recognized as safe for their intended use. However, by way of illustration, the Commissioner regards such common food ingredients as salt, pepper, vinegar, baking powder, and monosodium glutamate as safe for their intended use. This part includes additional substances that, when used for the purposes indicated, in accordance with good manufacturing practice, are regarded by the Commissioner as generally recognized as safe for such uses" (21 CFR §182.1).

The following regulations pertaining to affirmed GRAS substances obtained by physical separation from bovine milk suggest that the parent product, bovine milk itself, is GRAS as an ingredient in conventional foods.

21 CFR §184.1979(a)—reduced lactose whey, produced by removal of lactose by physical separation techniques (e.g., precipitation, filtration, dialysis)

21 CFR §184.1979(b)—reduced minerals whey, produced by removal of a portion of the minerals by physical separation techniques

21 CFR §184.1979(c)—whey protein concentrate, produced by physical separation of protein and non-protein constituents

21 CFR §184.1553—peptones, "a variable mixture of polypeptides, oligopeptides, and amino acids that are produced by partial hydrolysis of casein, …[1], or lactalbumin" using proteolytic enzymes.

The report listed below from the Select Committee on GRAS Substances and the six GRAS notices for milk-derived ingredients also suggest that bovine milk is regarded as GRAS.

SCOGS Report No. 37b—enzymatically hydrolyzed casein

GRN000011—mixture of calcium casein peptone and calcium phosphate

GRN000037—whey protein isolate

GRN000037—dairy product solids

GRN000052—whey mineral concentrate

GRN000196—bovine milk basic protein fraction

GRN000504—milk protein concentrate and milk protein isolate

Based on these references, it seems clear that dry whole milk is already GRAS as an ingredient in conventional foods; consequently, determination that it is GRAS, based on scientific procedures, as an ingredient in infant formula is properly regarded as an expansion of the allowable uses of an already GRAS ingredient rather than a novel GRAS determination.

[1] The ellipsis omits non-milk sources of peptones, including soy, gelatin, fatty tissue, and egg albumin.

6.2. Past Use of Whole Milk or Dry Whole Milk in Infant Feeding

While current recommendations dating back more than fifty years recommend against feeding 100% whole milk to infants from birth to one year of age as the sole source of nutrition because it does not provide optimal nutrition when consumed alone, there is a long record of safe consumption of whole milk during this period. Fomon (2001) reviewed infant feeding through the twentieth century. He noted that, in the early years of the century, "the majority of formula-fed infants received formulas made in the home from whole milk or 'top milk' (i.e., milk with 7-10% fat)." In the 1920s, "formulas made from whole milk with added Karo® syrup … provided nearly 100 kcal/dl." Whole milk or evaporated milk remained the usual base for infant formula through World War II. Fomon (2001): "From the 1930s or early 1940s, most formulas fed to infants in the United States were prepared by mixing evaporated milk or fresh cow's milk with water and adding carbohydrate. … Home-prepared formulas were sometimes made with cow's milk (usually pasteurized and homogenized) rather than with evaporated milk." In the 1950s, according to Fomon (2001), "it was the opinion of most physicians and the general public that formula feeding was about as safe and satisfactory as breast-feeding. However, … the low content of iron in the formulas together with the high intake of inhibitors of iron absorption were responsible for a high prevalence of iron deficiency."

Fomon (2001) cited survey data indicating that, in the 1960s, "60% of infants were fed whole milk by 4 months of age." In 1971, ">30% of infants from 3 to 4 months of age, >40% of infants from 4 to 5 months of age and >60% of infants from 5 to 6 months of age were fed cow's milk." Interest in breast feeding in the last thirty years of the twentieth century led to a deferment of the age of introduction of cow's milk, but "it was generally recommended (American Academy of Pediatrics Committee on Nutrition 1976) that for non-breastfed infants >6 months old, formula feeding was desirable, but cow's milk plus regular feeding of iron-fortified cereals was a satisfactory alternative."

6.3. Studies in Animals

Because cow's milk contains estrogens, progesterone, and insulin-like growth factor 1, which are associated with breast cancer, Nielsen et al. (2011) studied prepubertal exposure to whole milk in pregnant Sprague-Dawley rats. Pups were given either water or whole milk from post-natal day 14 to day 35 and mammary tumorigenesis was induced with 7,12-dimethylbenz[a]-anthracene on day 50. Rats exposed to milk before puberty exhibited reduced carcinogen-induced mammary carcinogenesis. The authors concluded that "drinking milk before puberty reduces later risk of developing mammary cancer in rats." Importantly, there was no suggestion that prepubertal consumption of whole milk increases the risk of cancer; further, test and control rats did not differ in weight gain and no adverse effects associated with milk feeding were reported.

Li et al. (2014) assigned 34 preterm Large White X Danish Landrace X Duroc piglets delivered by caesarean section at 105 days gestation to one of 3 feeding regiments in which they were fed via orogastric feeding tubes for 4 days. The feeding consisted of reconstituted whole milk powder (n = 15), infant formula (n = 10), or raw bovine milk (n = 9). Pigs were monitored every 3 hours for symptoms of necrotizing enterocolitis (NEC) such as abdominal distension lethargy, cyanosis, or bloody diarrhea. Pigs were euthanized on day 5 and intestinal tissue samples were taken. Pigs fed whole milk powder had significantly healthier intestinal structure (mucosal weight, villus height) and function (nutrient absorption, gut permeability, and reduced NEC severity) than those fed raw bovine milk, and both milk diets were superior to infant formula. No adverse effects associated with the interventions were reported.

6.4. Studies in Infants and Toddlers

Twenty-three studies were found in the literature in which whole milk was given to infants or toddlers. This includes 12 prospective, randomized, controlled clinical trials and a number of longitudinal or retrospective cohort studies. While safety was rarely the primary endpoint, the publications most often addressed reporting of adverse events. In none of these studies were any adverse events attributable to feeding of whole milk reported other than iron deficiency among children not receiving iron fortification or supplementation. These studies are summarized in Table 9.

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Alarcon et al. 1991	Prospective, randomized, multi-arm trial of the treatment of acute childhood diarrhea	85 Peruvian infants and children aged 5-24 months hospitalized for acute diarrhea	110 kcal/kg bw/day from: 1) Dried whole milk, potato flour, carrot flour, sucrose & veg oil 2) Wheat flour, pea flour, carrot flour, sucrose, & veg oil 3) Soy-protein isolate lactose-free formula	Children in all groups gained weight with no differences in anthropometric status, energy intakes, energy absorption, nitrogen retention, or fecal output and no differences in treatment failure. The authors concluded that "these locally available, low-cost staple food mixtures [i.e., interventions 1 and 2] offer a safe and nutritionally adequate alternative to a commercially produced lactose-free formula for the dietary management of young children with acute diarrhea in this setting."
Bonuck et al. 2014	Observational cohort study of dietary intake and overweight at 12 months of age	286 low-income infants and toddlers aged 12.6±0.5 months (186 normal, 100 overweight)	Measurements of dietary intake, anthropometrics, meal-time behavior	Normal weight and overweight toddlers did not differ in consumption of whole milk, mean daily energy intake, intake of fat, saturated fat, or protein. The total sample consumed a mean of 2.0±1.8 cups of whole milk per day. Whole milk consumption was lower in overweight vs. normal weight toddlers (1.7±1.8 vs. 2.1±1.8 cups/day). Thus, consumption of whole milk was not associated with overweight.
Brown et al. 1991	Prospective, randomized, double-blind, placebo-controlled trial of the management of acute childhood diarrhea	116 Peruvian male infants and toddlers aged 3-24 months with acute diarrhea	55 to 110 kcal/kg bw/day from: 1) Whole milk & wheat noodles 2) Lactose-hydrolyzed whole milk & wheat noodles 3) Modified whole milk 4) Lactose-hydrolyzed milk formula	The combination of milk and noodles resulted in reduced stool outputs, shorter durations of diarrhea, and lower rates of treatment failure than did milk alone. The authors concluded that "the noodle-milk diets employed during this study were safer than the milk diets for the dietary management of children with acute diarrhea."
Fomon et al. 1981	Prospective, randomized, placebo-controlled trial of whole-milk feeding in infancy	81 normal healthy infants aged 112 days	Given pasteurized whole milk (n = 39) or Enfamil (n = 42) for 12 weeks	Incidence of blood in stool was greater among infants fed whole milk from age 112 to 140 days; no difference thereafter. [N.B. No iron supplementation was provided.] No difference in mean hemoglobin, hematocrit, serum iron, total iron-binding capacity, or transferrin saturation.
Hertramph et al 1990	Prospective, randomized, placebo-controlled trial of fortification to prevent iron-deficiency	190 healthy infants	84 infants received whole milk supplemented with 15 mg ferrous sulfate & 100 mg ascorbic acid/100 g powder; 104 infants received the same milk with no supplement for 9 months	All iron nutritional parameters were higher in the supplemented group. Iron-deficiency anemia was reported in 34% of the control but 0% of the treatment group. The authors concluded that, "The product exhibited excellent tolerance and could therefore be used to eradicate iron-deficiency anemia of the infant."

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Hjelt et al 1989	Prospective, randomized, placebo-controlled trial of refeeding in acute pediatric gastroenteritis	52 infants and children aged 6-46 months hospitalized with acute gastro-enteritis after oral rehydration	Subjected to either rapid refeeding (lactose-treated whole milk as only fluid intake; n = 27) or gradual refeeding (fluids other than whole milk; n = 25) for 7 days	The two regimens produced similar results with regard to duration and severity of diarrhea and vomiting. The rapid-refeeding group derived more energy from fat and protein and less from carbohydrate than did the gradual-refeeding group. Milk provided 47-59% of the daily energy intake of the rapid-refeeding group. The authors reported that the whole milk was well accepted and no signs of cow's milk protein intolerance were observed. They suggested that the milk-based rapid-refeeding regimen can be employed "without the fear of negative effects on the outcome."
Houghton et al. 2011	Prospective, randomized, single-blind, placebo-controlled trial of vitamin D-fortified whole milk & 25-hydroxy-vitamin D level	181 healthy toddlers aged 12-20 months (mean age 17 months)	Toddlers received red meat or vitamin D-fortified whole milk for 20 weeks.	After 20 weeks, serum 25(OH)D concentrations but not parathyroid hormone were significantly raised in the milk group. The prevalence of having a serum 25(OH)D <50 nmol/L remained unchanged at 43% in the meat group, whereas it decreased to between 11 and 15% in those consuming fortified whole milk. The authors concluded that "habitual consumption of vitamin D-fortified milk providing a mean intake of nearly 4 µg/d was effective in achieving adequate year-round serum 25(OH)D for most children."
Isolauri et al. 1986	Prospective, randomized, placebo-controlled trial of refeeding in acute pediatric gastroenteritis	65 infants and toddlers (aged 14.7±7.2 months) hospitalized for acute gastro-enteritis	Refeeding included whole milk (n = 38) or no milk (n = 27)	The authors reported that, "There was no difference between the groups in the clinical recovery from diarrhea. No child had prolonged diarrhea. No new cases of clinical atopy were observed at 1-month follow-up, and there were no significant increases in the total or milk-specific IgE levels. Serum IgG and IgA antibodies to β-lactoglobulin and α-casein were initially present in the majority of the children, but there were no appreciable changes in these cow's milk antibodies after gastroenteritis regardless of the type of diet. It is concluded that cow milk and milk products can be safety given in acute gastroenteritis as parts of the mixed diet for children over 6 months of age."
Lamkjaer et al. 2009	Prospective, randomized, placebo-controlled trial of whole milk v. infant formula on growth and IgF-I	83 healthy infants	In a 2x2 design, infants received whole milk or infant formula, with or without fish oil	Intake of whole milk significantly increased protein energy percentage and serum urea nitrogen; there was no effect on anthropometric measures of growth. The whole-milk intervention increased IGF-I in boys but not in girls. Intake of fish oil had no effect on the outcomes. The authors concluded that, "Randomization to whole milk had no overall effect on growth. However, the positive effect of whole milk on IGF-I in boys and the positive association between protein energy percentage and IGF-I at 9 and 12 months is consistent with the hypothesis that a high milk intake stimulates growth."

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Maulen-Radovan et al. 1999	Prospective longitudinal study of the impact of fortified whole milk in children	227 generally healthy infants and children aged 8-60 months; included 45 malnourished & 36 anemic children	Toddlers and children consumed 500 ml fortified whole milk/day for 90 days	"The milk was well tolerated and widely accepted." Anthropometric measures, hemoglobin, serum iron, vitamin B12, and folic acid all increased. The authors concluded, "The consumption of a fortified whole milk during 90 days improved significantly the nutritional status of the children, the weight for height Z score, the plasma level of vitamin B12 and Hb, and decreased the number of anemic and malnourished children."
Penrod et al. 1990	Retrospective cohort study of infant formula vs. cow's milk in infancy	100 infants and toddlers aged 45.6±1.0 weeks	55 infants had been receiving infant formula for at least 3 months prior to enrollment; 45 infants had been receiving whole cow's milk	The infants receiving the fortified infant formula had significantly better iron status than those receiving whole milk and lower weight. [N.B. No iron supplementation was provided.] The two groups did not differ in other measures of nutritional status. The authors noted that some differences may result from differences in beikost rather than primary beverage.
Stekel et al. 1986	Mono-and double-isotopic analysis of iron absorption by infants con-suming different types of cows' milk formulas	364 infants and toddlers aged 5-18 months	Following an overnight fast, formulas containing $^{59}FeSO_4$ were fed by bottle; infants consumed 100-250 ml in a single bolus dose of one of 7 types of lowfat milk or one of 4 types of whole milk and iron absorption was measured	There was no significant difference in absorption of iron from the milk or from ferrous sulfate supplementation due to the level of milk fat. Iron absorption ranged from 2.9 to 5.1%, with no correlation with the milkfat content. These findings indicate that use of whole milk rather than lowfat milk in infant formula does not interfere with the absorption of iron from the formula.
Stekel et al. 1988.	Prospective, randomized, placebo-controlled trial of supplemented vs. unsupplemented whole milk	554 infants with birthweight >2500 g	276 infants received whole milk supplemented with ferrous sulfate & ascorbic acid for 12 months	The authors reported that, "the acceptability of this milk was excellent." 2.5% of infants in the group receiving whole milk + supplements had iron deficiency anemia compared with 25.7% of the control group.

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Svahn et al. 2000	Prospective, randomized, placebo-controlled trial of the effect of quantity and quality of fat	38 healthy infants and toddlers aged 12 months	Fed one of 4 milks for 6 months: 1) lowfat cow's milk 2) whole cow's milk 3) partially veg. fat milk 4) wholly veg. fat milk	There was a lower percentage of saturated fatty acids in plasma triacylglycerol in toddlers fed low-fat milk or milk with 50% or 100% vegetable fat than in children fed whole milk. Plasma polyunsaturated fatty acid levels were significantly higher in children fed milk with vegetable fat than in children fed whole milk. Blood lipid concentrations were lower in children fed milk with 50% vegetable fat. No adverse events were reported.
Thomas et al. 1986	Longitudinal cohort study of infant feeding and excretion of hemoglobin and α_1-antitrypsin (FA1AT)	820 healthy infants aged 2 weeks to 12 months	Infants were receiving: 1) whole milk (n = 146) 2) breast milk (n = 354) 3) infant formula (n = 320)	Levels of fecal hemoglobin and FA1AT were low in all groups and showed little difference by type of feeding. The authors reported that, "unrecognized intestinal abnormalities, as based on hemoglobin and FA1AT excretion, appear to be uncommon in healthy infants fed a balanced diet and fresh cow's milk. Human milk-fed infants had higher FA1AT concentrations than infants receiving formula or cow's milk. However, total daily FA1AT excretion was similar in all three milk-feeding groups. The differences in FA1AT concentration were a function of differences in daily stool output in response to diet." They concluded, "our data support the recent recommendation of the Committee on Nutrition of the American Academy of Pediatrics to allow introduction of pasteurized, fresh whole cow's milk into the diets of infants older than 6 months of age."
Torres et al. 1995	Longitudinal open-label study of iron-fortified whole milk and toddler's nutritional status	335 toddlers <2 years of age	Toddlers consumed dry whole milk fortified with 9 mg iron & 65 mg vitamin C/100 g for 6 months	Average hemoglobin increased from 10.4 to 11.6 g/dl. No intervention-associated adverse events were reported and the authors concluded that, "the utilization of enriched foods is an excellent alternative in the treatment of iron deficiency in populations of children under 2 years of age."
van der Gaag and Forbes 2014	Case-controlled retrospective study of a high-fat diet in children with non-specific elevated IgE	105 children aged 1-18 years (median age = 4.65 years) with non-specific elevated IgE	49 children were encouraged to consume at least 200 ml whole milk/day, beef, butter, and green vegetables, while 56 were not. Children were followed for 1 year.	The intervention group demonstrated a greater decrease in IgE (9.2 vs. 0.1 kU/L) and were more likely to report improvement in symptoms (53.2% vs. 28.6%). The authors concluded that, "Overall, the effects of nutrients and vitamins on the decrease in IgE are promising." They did not report any intervention-associated adverse events.

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
van der Gaag et al. 2017	Retrospective cohort study of a high-saturated-fat diet in children	121 children aged 1-16 years (median age = 3.6 years)	All children received dietary advice to consume whole milk, beef, butter, and green vegetables. 55 of them adhered to the advice, while 66 did not. Measures were taken over 3 months	In the group following the advice to consume a diet high in saturated fat, including whole milk, there was a significant reduction in the cholesterol/HDL ratio and non-HDL-cholesterol and an increase in HDL-cholesterol, while there was no difference in the BMI and BMI z-scores. The authors reported that, "The dietary advice has no adverse effect on the lipid profile, BMI, and BMI z-scores in children, but has a significant beneficial effect on the cholesterol/HDL ratio, non-HDL-cholesterol, and the HDL-cholesterol," and concluded, "The dietary advice can, therefore, be safely recommended and might be beneficial for children with recurrent respiratory tract infections."
van der Gaag et al. 2020	Prospective, randomized, controlled trial of a high-saturated-fat diet in pediatric upper respiratory tract infections	118 toddlers aged 1-4 years (mean age = 2.4±1.1 years) with recurrent upper respiratory tract infections	58 children were encouraged to consume at least 300 ml whole milk/day, beef, butter, and green vegetables, while 60 were not. Children were followed for 6 months.	Children in the dietary advice group had a mean of 4.8 days per month with symptoms of an upper respiratory tract infection in the last three months of the study, compared to 7.7 in the control group. The use of antibiotics was significantly reduced in the dietary advice group. No adverse events were reported. The authors suggested that "this diet provides parents with a tool to improve the health of their children."
Vanderhout et al. (2016a)	Cross-sectional analysis of milk-fat percentage and BMI in early childhood	2745 healthy urban toddlers and children aged 12-72 months	Adjusted bivariate linear regression of milk-fat percentage and BMI z-score and 25-hydroxyvitamin D status	Children who drank whole milk had a 5.4-nmol/L higher median 25(OH)D concentration and a 0.72 lower BMI z-score than children who drank 1% milk. The authors concluded that, "Whole milk consumption among healthy young children was associated with higher vitamin D stores and lower BMI."
Vanderhout et al. (2016b)	Cross-sectional analysis of milk-fat percentage and 25-hydroxyvitamin D in childhood	2857 healthy urban toddlers and children aged 12-72 months	Adjusted multivariate linear regression of milk-fat percentage and milk volume and 25-hydroxyvitamin D status	Children who drank 1% milk needed 2.46 cups of milk to have the 25(OH)D status of children who drank 1 cup of whole milk. Children who consumed 1% milk had 2x higher odds of having a 25(OH)D concentration <50 nmol/L than children who consumed whole milk. The authors concluded that "recommendations for children to drink lower-fat milk (1% or 2%) may compromise serum 25(OH)D levels and may require study to ensure optimal childhood health."
Wong et al. 2019	Longitudinal study of milk fat intake and non-HDL in young children	2890 children aged 2-8 years	Statistical analyses of the relationship between cow's milkfat intake and serum non-HDL cholesterol concentration	There was a small positive correlation between milkfat intake and non-HDL cholesterol, but not with the odds of having high non-HDL cholesterol. The authors concluded that the correlation exists, but with no indication of leading to high non-HDL cholesterol.

Table 9. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Ziegler et al. 1990	Prospective, randomized, placebo-controlled trial of infant feeding and GI blood loss	52 healthy term infants aged 24 weeks	26 infants each were assigned to receive whole cow's milk or infant formula for 12 weeks.	There were no differences between groups in parental reports of regurgitation, vomiting, constipation, or other feeding-related behavior. Stool hemoglobin concentration increased with the introduction of whole cow milk from 622±527 µg/g dry stool at baseline to 3598± 10,479 µg/g dry stool during the first 28 days of Ingestion of whole cow milk. Among infants fed formula, stool hemoglobin did not Increase and was significantly less than in the whole milk group. Stools with occult blood increased from 3.0% at baseline to 30.3% in the whole-milk group during the first 28 days of the trial, whereas the proportion of positive stools remained low (5.0%) with the feeding of formula. The proportion of occult-blood-positive stools among whole-milk-fed infants declined later, but for the entire trial it remained significantly elevated. The authors concluded that, "a large proportion of normal nonanemic infants respond to the feeding of pasteurized cow milk [i.e., whole milk as the sole source of nutrition and no added iron] with increased fecal loss of blood."

6.5. Safety Assessment and GRAS Determination

This section presents an assessment that demonstrates that the intended use of dry whole milk in nonexempt infant formula is safe and is GRAS based on scientific procedures.

This safety assessment and GRAS determination entail two steps. In the first step, the safety of the intended use of dry whole milk is demonstrated. Safety is established by demonstrating a reasonable certainty that the exposure of infants and toddlers to dry whole milk under its intended conditions of use is not harmful. In the second step, the intended use of dry whole milk is determined to be GRAS by demonstrating that the safety of this substance under its intended conditions of use is generally recognized among qualified scientific experts and is based on generally available and accepted information.

The regulatory framework for establishing whether the intended use of a substance is GRAS, in accordance with Section 201(s) of the Federal Food Drug and Cosmetic Act, is set forth under 21 CFR §170.30. This regulation states that general recognition of safety may be based on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. A GRAS determination may be made either: 1) through scientific procedures under §170.30(b); or 2) through experience based on common use in food, in the case of a substance used in food prior to January 1, 1958, under §170.30(c). This GRAS determination employs scientific procedures established under §170.30(b).

A scientific procedures GRAS determination requires the same quantity and quality of scientific evidence as is needed to obtain approval of the substance as a food additive. In addition to requiring scientific evidence of safety, a GRAS determination also requires that this scientific evidence of safety be generally known and accepted among qualified scientific experts. This "common knowledge" element of a GRAS determination consists of two components:

1. Data and information relied upon to establish the scientific element of safety must be generally available; and
2. There must be a basis to conclude that there is a consensus among qualified experts about the safety of the substance for its intended use.

The criteria outlined above for a scientific-procedures GRAS determination are applied below in an analysis of whether the intended use of dry whole milk in nonexempt infant formula is safe and is GRAS.

6.5.1. Evidence of Safety

Whole milk and dry whole milk are widely consumed by infants, toddlers, children, and adults with no adverse effects specifically attributable to whole milk other than allergic reactions in susceptible individuals. Over many years prior to the 1970s during which whole milk was widely used as a sole source of nutrition for infants, there was no reported pattern of adverse effects and no evidence of malnutrition other than iron deficiency.

The many controlled studies of feeding of whole milk to infants and toddlers elicited no reports of adverse effects. In a number of studies in which nutrition with unfortified whole milk was compared with iron-fortified infant formula, the latter usually resulted in superior iron status. This deficiency, it was shown, is remedied by fortifying or supplementing the milk with iron. Thus, this finding that unfortified milk alone may not provide adequate iron has no relevance to the intended use of dry whole milk by ByHeart, which is as a component of infant formula with iron rather than as a stand-alone source of infant nutrition.

In summary, the body of generally available evidence from history of use and controlled scientific studies supports the safety of By Heart's intended use of dry whole milk.

6.5.2. Conclusion of the GRAS Panel

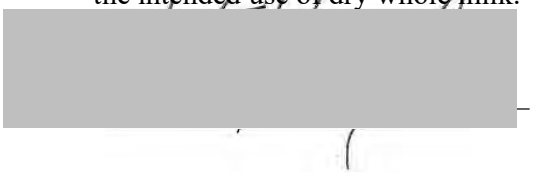
The intended addition of dry whole milk to nonexempt infant formula has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(b). This safety was shown by animal studies in rats and pigs; uncomplicated human digestion via well-established metabolic pathways without adverse effects; current safe consumption of whole milk and dry whole milk including consumption by infants, toddlers, and children; and controlled clinical trials showing no adverse effects associated with consumption of whole milk or dry whole milk by infants or toddlers. Finally, because this safety assessment satisfies the common knowledge requirement of a GRAS determination, this intended use is GRAS.

Determination of the safety and GRAS status of the intended use of dry whole milk has been made through the deliberations of a GRAS Panel consisting of Ronald Kleinman, M.D., Berthold V. Koletzko, M.D., Ph.D., and Robert J. Nicolosi, Ph.D. These individuals, qualified by scientific training and experience to evaluate the safety of food ingredients intended for addition to infant formula, independently and collectively critically evaluated the publicly available information on the safety of whole milk and dry whole milk and the potential exposure to infants and toddlers anticipated to result from its intended use. They individually and collectively determined that no evidence exists in the available information on whole milk and dry whole milk that demonstrates, or suggests reasonable grounds to suspect, a hazard to infant or toddlers under the intended conditions of use of dry whole milk.

It is the GRAS Panel's opinion that other qualified scientists reviewing the same publicly available data would reach a similar conclusion regarding the safety of dry whole milk under its intended conditions of use. Therefore, the intended use of dry whole milk in nonexempt infant formula intended for consumption by healthy term infants from the first day of life is GRAS by scientific procedures.

6.6. Statement Regarding Information Inconsistent with GRAS

I have reviewed the available data and information and am not aware of any data or information that are, or may appear to be, inconsistent with our conclusion of the GRAS status of the intended use of dry whole milk.



6.7. Statement of the GRAS Panel

We, the undersigned members of the GRAS Panel, are qualified by scientific education and experience to evaluate the safety of substances intended for addition to infant formula. We have critically evaluated the publicly available information on dry whole milk and have individually and collectively determined that no evidence exists in the available information on dry whole milk that demonstrates, or suggests reasonable grounds to suspect, a hazard to infants or toddlers under the intended conditions of use of dry whole milk.

We unanimously conclude that the intended addition of dry whole milk, produced consistent with current good manufacturing practice (cGMP) and meeting the food-grade specifications presented in this monograph, to nonexempt infant formula intended for consumption by healthy term infants from the first day of life, at the level specified in the monograph, is safe and is GRAS by scientific procedures.

It is our opinion that other qualified and competent scientists reviewing the same publicly available information would reach a similar conclusion.

Ronald Kleinman, M.D.
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Signature:  Date: 11/16/2020

Berthold V. Koletzko, Dr med, Dr med habil (M.D., Ph.D.)
Professor of Pediatrics
University of Munich
Munich, Germany

Signature: _____ Date: _____

Robert J. Nicolosi, Ph.D.
Professor Emeritus
University of Massachusetts—Lowell
Lowell, Massachusetts

Signature: _____ Date: _____

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We unanimously conclude that the intended addition of dry whole milk, produced consistent with current good manufacturing practice (cGMP) and meeting the food-grade specifications presented in this monograph, to nonexempt infant formula intended for consumption by healthy term infants from the first day of life, at the level specified in the monograph, is safe and is GRAS by scientific procedures.

It is our opinion that other qualified and competent scientists reviewing the same publicly available information would reach a similar conclusion.

Ronald Kleinman, M.D.
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Signature: _____ Date: _____

Berthold V. Koletzko, Dr med, Dr med habil (M.D., Ph.D.)
Professor of Pediatrics
University of Munich
Munich, Germany

Signature: _____ Date: 14 Nov. 2020

Robert J. Nicolosi, Ph.D.
Professor Emeritus
University of Massachusetts—Lowell
Lowell, Massachusetts

Signature: _____ Date: _____

6.7. Statement of the GRAS Panel

We, the undersigned members of the GRAS Panel, are qualified by scientific education and experience to evaluate the safety of substances intended for addition to infant formula. We have critically evaluated the publicly available information on dry whole milk and have individually and collectively determined that no evidence exists in the available information on dry whole milk that demonstrates, or suggests reasonable grounds to suspect, a hazard to infants or toddlers under the intended conditions of use of dry whole milk.

We unanimously conclude that the intended addition of dry whole milk, produced consistent with current good manufacturing practice (cGMP) and meeting the food-grade specifications presented in this monograph, to nonexempt infant formula intended for consumption by healthy term infants from the first day of life, at the level specified in the monograph, is safe and is GRAS by scientific procedures.

It is our opinion that other qualified and competent scientists reviewing the same publicly available information would reach a similar conclusion.

Ronald Kleinman, M.D.
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Signature: _____ Date: _____

Berthold V. Koletzko, Dr med, Dr med habil (M.D., Ph.D.)
Professor of Pediatrics
University of Munich
Munich, Germany

Signature: _____ Date: _____

Robert J. Nicolosi, Ph.D.
Professor Emeritus
University of Massachusetts—Lowell
Lowell, Massachusetts

Signature:  Date: November 13, 2020

Part 7: List of Supporting Data and Information

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE (Subpart E of Part 170)

Form Approved: OMB No. 0910-0342; Expiration Date: 07/31/2022
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000980	Nov 20, 2020
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration,5001 Campus Drive, College Park, MD 20740-3835.

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* 2020-11-04

4 For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Gyan Rai	Director, Regulatory

Organization *(if applicable)*: ByHeart, Inc.

Mailing Address *(number and street)*: 689 5th Avenue 14th Floor

City	State or Province	Zip Code/Postal Code	Country
New York	New York	10022	United States of America

Telephone Number	Fax Number	E-Mail Address
978-400-9668		gyan@byheart.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position or Title
James T. Heimbach	President

Organization *(if applicable)*: JHeimbach LLC

Mailing Address *(number and street)*: 923 Water Street #66

City	State or Province	Zip Code/Postal Code	Country
Port Royal	Virginia	22535	United States of America

Telephone Number	Fax Number	E-Mail Address
8047425543		JH@JHEIMBACH.COM

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

1. Name of notified substance, using an appropriately descriptive term

Dry whole milk

2. Submission Format: *(Check appropriate box(es))*

☒ Electronic Submission Gateway

☐ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

4. Does this submission incorporate any information in CFSAN's files? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for conclusions of GRAS status *(Check one)*

☒ Scientific procedures *(21 CFR 170.30(a) and (b))* ☐ Experience based on common use in food *(21 CFR 170.30(a) and (c))*

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

SECTION D – INTENDED USE

1. Describe the intended conditions of use of the notified substance, including the foods in which the substance will be used, the levels of use in such foods, and the purposes for which the substance will be used, including, when appropriate, a description of a subpopulation expected to consume the notified substance.

As a nutritive ingredient in non-exempt infant formula intended for consumption by healthy term infants from the first day of life.

2. Does the intended use of the notified substance include any use in product(s) subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☒ No

3. If your submission contains trade secrets, do you authorize FDA to provide this information to the Food Safety and Inspection Service of the U.S. Department of Agriculture?

(Check one)

☐ Yes ☐ No , you ask us to exclude trade secrets from the information FDA will send to FSIS.

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

(check list to help ensure your submission is complete – PART 1 is addressed in other sections of this form)

☒ PART 2 of a GRAS notice: Identity, method of manufacture, specifications, and physical or technical effect (170.230).

☒ PART 3 of a GRAS notice: Dietary exposure (170.235).

☒ PART 4 of a GRAS notice: Self-limiting levels of use (170.240).

☒ PART 5 of a GRAS notice: Experience based on common use in foods before 1958 (170.245).

☒ PART 6 of a GRAS notice: Narrative (170.250).

☒ PART 7 of a GRAS notice: List of supporting data and information in your GRAS notice (170.255)

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☐ Yes ☒ No

Did you include this other information in the list of attachments?

☐ Yes ☐ No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that James T. Heimbach
(name of notifier)

has concluded that the intended use*(s)* of dry whole milk
(name of notified substance)

described on this form, as discussed in the attached notice, is (are) not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is generally recognized as safe recognized as safe under the conditions of its intended use in accordance with § 170.30.

2. ByHeart, Inc. *(name of notifier)* agrees to make the data and information that are the basis for the conclusion of GRAS status available to FDA if FDA asks to see them; agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so; agrees to send these data and information to FDA if FDA asks to do so.

Office of JHeimbach LLC, 923 Water Street, Port Royal VA 22535
(address of notifier or other location)

The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information provided herein is accurate and complete to the best or his/her knowledge. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

3. Signature of Responsible Official, Agent, or Attorney	**Printed Name and Title**	**Date (mm/dd/yyyy)**
	James T. Heimbach, President, JHeimbach LLC	11/16/2020

SECTION G – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Form3667.pdf	Administrative
	ByHeartGRASNotice.pdf	Administrative
	SignatureKleinman.pdf	Administrative
	SignatureKoletzko.pdf	Administrative
	SignatureNicolosi.pdf	Administrative

From: jheimbach@va.metrocast.net
To: Morissette, Rachel
Subject: [EXTERNAL] RE: questions for GRN 000980 - dry whole milk
Date: Friday, April 16, 2021 12:06:17 PM
Attachments: Morissette Rachel 20210416.pdf
OFAS GRN980 Response.pdf
Eurofins AOAC Methods Review.pdf
Milk Supplier"s Certificate.pdf

Dear Rachel—

Our response to the questions the FDA reviewers asked concerning ByHeart's GRAS notice GRN980 for the use of dry whole milk as a component of infant formula is attached. There are four documents:

- A cover letter addressed to you
- Our responses to the questions
- A review by Eurofins of the analytical methods of their analyses
- A certification by the milk supplier of compliance with the PMO

We are confident that we have satisfactorily addressed the issues raised by FDA, and will be happy to clarify anything that is not clear.

We are also pleased that we were able to respond within the ten business days you requested.

Best wishes for a good weekend—
Jim

James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal VA 22535
USA
Tel: (+1) 804-742-5543
Cell: (+1) 202-320-3063
Email: jh@jheimbach.com

JHeimbach LLC

April 16, 2021

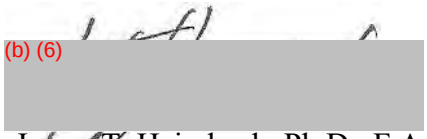
Rachel Morissette, Ph.D.
Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park MD 20740

Dear Dr. Morissette:

This letter is ByHeart's response to the questions posed by FDA reviewers regarding GRN 980 and sent to us on April 2, 2021.

We have begun our responses to each question on a new page to simplify your task of sorting them out. In addition to the responses that follow, we have attached to our email two documents that could not be pasted into our response, Eurofins AOAC Methods Review, which discusses the analytical methods used, and a Milk Supplier's Certificate that addresses the sourcing of our milk and its compliance with Pasteurized Milk Ordinance requirements. (This latter document is redacted to maintain the confidentiality of the supplier.)

We are confident that we have provided satisfactory responses to your questions. If anything is unclear, we will be happy to provide explanation.



James T. Heimbach, Ph.D., F.A.C.N.
President

cc. Jeanne Hoskin, Ph.D.
Gyan Rai, Ph.D.
ByHeart, Inc.

923 Water Street #66, Port Royal Virginia 22535, USA
tel. (+1) 804-742-5548 cell (+1) 202-320-3063 jh@jheimbach.com

1. On p. 19 of the notice, we note three regulations incorrectly cited for reduced lactose whey, reduced minerals whey, and whey protein concentrate. The use of the parentheses around the letters actually points to the conditions of use (a), (b), and (c) for whey only under 21 CFR 184.1979. The correct citations for the above-mentioned substances would be as follows:
   21 CFR 184.1979a – reduced lactose whey
   21 CFR 184.1979b – reduced minerals whey
   21 CFR 184.1979c – whey protein concentrate

   Response:
   Thank you for providing the correct citations for these substances that are listed on p 19 of the notice. We confirm they are:

   21 CFR 184.1979a – reduced lactose whey
   21 CFR 184.1979b – reduced minerals whey
   21 CFR 184.1979c – whey protein concentrate

Chemistry:

2. The intended use and technical effect of ByHeart's dry whole milk is unclear and is described a few different ways in the notice. ByHeart states the intended use on p. 4 (1.4. Intended Conditions of Use) as "a component of non-exempt infant formula intended for consumption by healthy term infants from the first day of life," on p. 12 (2.4. Technical Effect) as "a source of protein…not intended to serve any function other than nutrition," and on p. 13 (3.1. Intended Conditions of Use) "to provide nutrients more closely resembling those found in breast milk." Please clarify ByHeart's intended use and technical effect of dry whole milk.

Response:

The intended use and technical effect of ByHeart's dry whole milk should be revised as follows:

- p. 4 (1.4 Intended Conditions of Use) of dry whole milk when added at maximum use level of 16 g/100g powder is as an ingredient in ByHeart's whey-based, non-exempt infant formula when fed as a sole source of nutrition from the first day of life to healthy term infants.
- p. 13 (3.1. Intended Conditions of Use) of dry whole milk when added at maximum use level of 16 g/100g powder is as an ingredient in ByHeart's whey-based, non-exempt infant formula when fed as a sole source of nutrition from the first day of life to healthy term infants.
- p. 12 (2.4 Technical Effect) of dry whole milk when added at maximum use level of 16 g/100g powder as an ingredient in ByHeart's whey-based, non-exempt infant formula, when fed as a sole source of nutrition from the first day of life to healthy term infants, is the contribution of approximately 26% of the formula protein and other nutrients including 8% of formula lactose, 12% of formula fat, and minor amounts of vitamins and minerals.

Dry whole milk is not intended as the sole source of protein or fat in ByHeart's infant formula.

3. ByHeart states that the maximum intended use level of dry whole milk in powdered infant formula is 16 g/100 g and is equivalent to 2 g/100 mL of formula ready to consume based on a hydration rate of 12.5 g formula powder/100 mL formula ready to consume. The estimated dietary exposure reported in the notice is based, in part, on an assumed caloric content of 67 kcal/100 mL formula ready to consume. Please confirm the maximum intended use level of dry whole milk on a kilocalorie basis (i.e., 3 g/100 kcal).

Response:

We confirm that the intended use level of dry whole milk on a kilocalorie basis is 3 g/100 kcal.

The calculation is: (0.16 g dry whole milk/g formula powder x 12.5 g formula powder/67 kcal = 2 g dry whole milk/67 kcal = 3 g dry whole milk/100 kcal).

4. ByHeart calculates the 90th percentile dietary consumption of infant formula based on a caloric density of 67 kcal/100 ml of formula ready to consume and published estimates of the 90th percentile energy intake (i.e., 141.3 kcal/kg body weight (bw) for infant boys and 138.9 kcal/kg bw for infant girls). The calculated 90th percentile intakes are reported as 209.0 mL/kg bw and 205.5 mL/kg bw for boys and girls, respectively. We note that using the reported values, the calculated estimates should be 210.9 and 207.3 kcal/kg bw, respectively. Based on the results, it appears that a caloric density of 67.6 kcal/100 mL was used. Please confirm if this accurate.

   Response:
   FDA's calculation is correct. I have used this calculation in a number of GRAS notices since 2009. When I first did the calculation in 2009, it was based on a caloric density of 67.6 kcal/100 ml (as FDA calculated). However, since the caloric density of the formula of current interest is 67 rather than 67.6 kcal/100 ml, the amount of formula needed to achieve the stated caloric intakes is 210.9 and 207.3 ml/kg bw/day.

5. To describe the composition of dry whole milk, ByHeart references data from the U.S. Department of Agriculture's Nutrient Database for Standard Reference (USDA, 2020) and notes an expectation of variability in the concentrations of constituents that would be present in the notified substance that is not reflected in the USDA data.

   - The citation provided in the notice (USDA, 2020. Nutrient database for standard reference. https://fdc.nal.usda.gov/download-datasets.html) does not include the FDC ID number. The data provided appear to match those for FDC ID 173454 (Milk, dry, whole, without added vitamin D; SR legacy, released 2018); however, we note the most recent release (FDC ID 1097874, Milk, dry, not reconstituted, whole, published 10/30/2020) includes differences such as content of vitamin D (D2 + D3) (10.5 IU/100g) compared to data presented (20 IU/100 g).
   - Please clarify that the data presented are representative of the notified substance.
   - Please provide a characterization of the protein and fat of the notified substance.

   Response:
   To describe the composition of dry whole milk, ByHeart references data from the U.S. Department of Agriculture's Nutrient Database for Standard Reference (USDA, 2020) and notes an expectation of variability in the concentrations of constituents that would be present in the notified substance that is not reflected in the USDA data.

   As FDA observes, our reference for Table 1 in the notice, on pp. 6-8, was FDC ID 173454, denoted "Milk dry, not reconstituted, whole, without added vitamin D." At the time the GRAS notice was prepared, this was the most recent release. (The release cited by FDA was published on October 30, 2020. By that date, the notice had been written and was in the hands of the GRAS Expert Panel for review. It was sent to FDA on November 16, following revisions suggested by the Expert Panel and their signing the conclusion statement.)

   The revised USDA table cited by FDA introduced a small number of changes in the minerals and vitamins, as follows:
   - Manganese is no longer reported; it was given as 0.04 mg/100 g in the earlier release
   - Pantothenic acid is no longer reported; it was previously given as 2.271 mg/100 g
   - Choline concentration was revised from 117.4 to 119.3 mg/100 g
   - Vitamin A in IU is no longer reported; it was previously given as 934 IU/100 g
   - Vitamin D (D2+D3) was revised from 0.5 to 10.5 µg/100 g
   - Vitamin D (D2+D3) in IU is no longer reported; it was previously given as 20 IU/100 g
   - Vitamin D3 is no longer reported; it was previously given as 0.5 µg/100 g

   Since the notified substance is dry whole milk not differing from the milk sampled by the USDA except for the requirement of passing more stringent purity standards, these data on proximates, vitamins, and minerals are representative of the notified substance.

   The protein and fat of the notified substance are characterized in Table 1, which provides the breakout of amino acids and fatty acids reported by USDA. (These data, incidentally, are no longer reported in the FDC database.) As shown, the most prevalent amino acid is glutamic acid at 5.512 g/100 g, followed by leucine (2.578 g), proline (2.549g), lysine (2.087 g), and aspartic acid (1.997 g). Most of the fat is present as saturated fatty acids (16.742 g/100 g), primarily

hexanoic (7.522 g), octanoic (2.853 g), and tetranoic (2.82 g) acids. Monounsaturated fatty acids are present at about half the concentration of saturated fatty acids (7.924 g/100 g), primarily in the form of oleic acid (6.192g/100 g). Less than 1 g of polyunsaturated fatty acids are present in 100 g dry whole milk.

Data on phospholipids, sphingomyelin, and trans-fatty acids are presented in response to Q6.

6. ByHeart provides estimates of dietary exposure to various phospholipids, sphingomyelin, and trans-fatty acids based on the intended use and analytical data for the concentrations of these constituents of dry whole milk. The concentrations of these constituents are not discussed in the composition or specification sections of the notice. Please discuss any limits for these constituents and information on the analytical data used: for example, number of manufactured lots tested and methodology used.

Response:

The data were collected for the 3 lots tested and the average value was used for the nutritional profile represented in Table 6 in the notice. All samples were analyzed by Eurofins using validated methods appropriate for phospholipid analyses. Milk samples are prepared for NMR analysis using a microwave extraction method in a ternary solvent mixture (chloroform, methanol, and water). Phospholipids are concentrated in the organic layer, and we obtain a 31P-NMR spectrum of the organic layer to identify and quantify the phospholipids. The full set of lots tested are provided in Tables 1 and 2 below.

Table 1: Composition of Phospholipids in Dry Whole Milk

Phospholipids		MO19-0019	MO20-0014	MO20-0015	Average*	Dry Whole Milk Powder in Soga et al. (2015)[1]
Phosphatidylcholine (PC)	%	0.070	0.12	0.11	**0.10**	0.067
Phosphatidylethanoalmine (PE)	%	0.040	0.090	0.090	**0.073**	0.064
Phosphatidylinositol (PI)	%	0.020	0.030	0.030	**0.027**	0.037
Phosphatidylserine (PS)	%	0.020	0.050	0.050	**0.040**	0.033
Sphingomyelin (SM)	%	0.070	0.12	0.12	**0.10**	0.057
Other	%	0.020	0.020	0.020	**0.020**	0.028
Total	%	0.24	0.430	0.420	**0.363**	0.286
*** Average results of 3 lots**						

[1] Soga S, N Ota, A Shimotoyodome. 2015. Dietary milk fat globule membrane supplementation combined with regular exercise improves skeletal muscle strength in healthy adults: a randomized double-blind, placebo-controlled, crossover trial. *Nutr J* 14:85.

Table 2: Composition of Milk Fat Components

Composition of Milk fat components		MO19-0019	MO20-0014	MO20-0015	Average*	Breastmilk Composition in Ma et al. (2017)[2]
Butyric Acid	%	1.20	1.33	1.32	**1.28**	0.0009 - 0.76
Trans Fatty acid	%	1.35	2.32	2.33	**2.00**	1.9
CLA	%	0.33	0.54	0.55	**0.47**	0.07-0.49
C:15.0 Pentadecanoic:	%	0.47	0.40	0.40	**0.42**	0.08 - 0.5
C:17.0 Heptadecanoic	%	0.26	0.22	0.22	**0.23**	0.19 - 0.41
Cholesterol (mg/100g)	%	1.07	0.99	0.99	**1.02**	9 -20
*** Average results of 3 lots**						

The dry whole milk is not enriched for any components, and therefore the dry whole milk contains nutrients at levels naturally occurring in liquid whole milk that is only pasteurized and spray dried. The liquid milk is obtained from cows that are grass-fed; milk is collected from different farms and pooled together by the liquid milk supplier. The lipid, including phospholipid, is at naturally occurring levels, and as demonstrated by the analytical values for these in ByHeart's infant formula as tested by the same analytical method and the same external laboratory (Table 6 of the notice), their contribution in the finished infant formula is negligible and at levels comparable to that of human milk and commercial US infant formula. The phospholipid content of the dry whole milk is within the range reported in literature and consistent with natural composition of bovine milk[1,3].

[2] Ma L, AKH MacGibbon, HJBJ Mohamed, SL Loy, A Rowan, P McJarrow, BY Fong. 2017. Determination of phospholipid concentrations in breast milk and serum using a high-performance liquid chromatography - mass spectrometry-multiple reaction monitoring method. *Int Dairy J* 71:50-59.

[3] Jensen RG. 2002. The composition of bovine milk lipids: January 1995 to December 2000. *J Dairy Sci* 85:295–350.

7. The specified concentrations are listed as "typical concentration" for multiple constituents of the notified substance in Table 2 on p. 10 of the notice. Please clarify the typical concentration or range of concentrations that are considered acceptable for these specifications.

Response:

The specifications in Table 2 in the notice have been revised with the typical concentration or range of concentrations that are considered acceptable for these specifications, see Revised Table 2, below. (This table also provides answers to questions 7, 8, 9, 10, 11, 13, and 14).

Revised Table 2. Analyses of Three Non-Consecutive Lots of Dry Whole Milk Against Specifications.

Parameter	Specification	Lot Tested			Method (Eurofins)
		MO19-0019	MO20-0014	MO20-0015	
Moisture (%)	NMT[1] 5.0	2.30	3.13	3.07	M100_T100 (AOAC 925.09 / 926.08)
Protein (%)	NLT[2] 22 NMT 30	25.3	25.0	25.0	DGEN_S (AOAC 968.06 / 992.15)
Fat (%)	NLT 26 NMT 40	32.9	32.0	31.8	FAT_BH_S (AOAC 989.05/932.05/986.25/945.48B)
Titratable acidity (%)	NMT 0.15	<0.15	<0.15	<0.15	QA-PL-10.000 (USDA 918RL)
Peroxide value (meq/kg fat)	NMT 5	1.0	2.9	2.1	AOAC 965.33
Scorched Particle (mg)	NMT Disk B of ADPI (15 mg)	<7.5	<7.5	<7.5	USDA 918-RL; ADPI
Solubility	Pass / Fail	Pass	Pass	Pass	Internal Method (QA-PL-25.000)[3]
Cholesterol (mg/100 g)	NMT 150	107	99.0	99.2	CHOK-S (AOAC 994.10)
Ash (%)	NMT 7	5.2%	5.2%	5.2%	ASHM_S (AOAC 923.03)
Vitamin A (IU/100 g)	NMT 2000	804	943	914	VALC_S (AOAC 992.04/992.06/2001.13)
Vitamin D3 (IU/100 g)	NMT 20	<4	<4	<4	VDMS_S (AOAC 2011.11)
Iron (mg/g)	NMT 0.01	0.003	0.003	0.003	ICP_S (AOAC 984.27 / 985.01/2011.14)
Iodide (µg/g)	NMT 10	3.32	1.11	1.11	IODICPMS_S (AOAC 2012.15)
Sodium (mg/g)	NMT 10	3.01	2.94	2.92	ICP_S (AOAC 984.27 / 985.01/2011.14)
Potassium (mg/g)	NMT 20	11.06	10.81	10.75	ICP_S (AOAC 984.27 / 985.01/2011.14)
Chloride (mg/g)	NMT 20	7.97	7.19	7.15	CL_SALT_S (AOAC 963.05/971.27/986.26)
Selenium (µg/g)	NMT 1.2	0.120	0.703	0.715	SEIF_S (AOAC 2011.19)
Heavy metals					
Arsenic (µg/kg)	NMT 500	<10	<10	<10	ICP-MS (AOAC 2011.19 / 993.14)
Cadmium (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Lead (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Mercury (µg/kg)	NMT 50	<5	<5	<5	ICP-MS (AOAC 2011.19 / 993.14)
Microbiological					
Aerobic Plate Count (cfu[4]/g)	NMT 10,000	160	60	50	APC (AOAC 966.23)
Coliforms (cfu/g)	NMT 10	<10	<10	<10	CMMEF Chapter 8.7
Mold (cfu/g)	NMT 50	<10	<10	<10	FDA BAM Chapter 18 mod.
Yeast (cfu/g)	NMT 50	<10	<10	<10	FDA BAM Chapter 18 mod.

B. cereus (cfu/g)	NMT 100	<10	<10	<10	FDA BAM Chapter 14
Enterobacteri-aceae (cfu/g)	NMT 10	<10	<10	<10	CMMEF Chapter 9.62
S. aureus	NMT 10	<10	<10	<10	BAM Chapter 12
Listeria spp. (in 25 g)	Negative	Not detected	Not detected	Not detected	BAX PCR detection, method AOAC-RI 050903 *Listeria* spp is per BAM Chapter 10
Salmonella LAMP detection (in 25 g)	Negative	Not detected	Not detected	Not detected	SALLAMP (AOAC 2016.01)
Cronobacter species D (in 10 g)	Negative	Not detected	Not detected	Not detected	BAX® System PCR Assay for E. sakazakii (Cronobacter) *Cronobacter* spp per BAM Chapter 29

1. NMT = not more than
2. NLT = not less than
3. Solubility Index (ml)- USDA 918-RL, ADPI NMT 1.0 ml will be implemented prior to commercial production
4. cfu = colony-forming units

8. The specification for titratable acidity is listed as not less than 15%. We note, for example, that the limit for titratable acidity specified in the USDA's "United States Standards for Grades of Dry Whole Milk"[1] is ≤0.15% and ≤0.17% for "extra" grade and "standard" grade dry whole milk, respectively. Please confirm that the specification in the notice is correct.

Response:
This was a typographical error - we apologize for the oversight. The value is NMT 0.15% for our grade A dry whole milk. See updated Table 2 in the response to Q7.

9. Specifications for dry whole milk in the USDA Standards include scorched particle content and solubility index. These specifications are not included in the notice for dry whole milk. Please include these specifications with at least three non- consecutive batch analyses.

Response:

Please note that the Pennsylvania Department of Agriculture (PDA) is present on-site during production of our dry milk and evaluates temperature and processing conditions in accordance with Pasteurized Milk Ordinance (PMO) requirements.

Our manufacturing facility has a permit from the PDA to manufacture grade A dairy products. Furthermore, a letter of certification is on file related to the confirmation of routine inspections, conformance of sanitation requirements, and permit for production and sale of milk products in the state of Pennsylvania. Currently, the grade A dry whole milk produced will be consumed as a raw material component in the future ByHeart Infant Formula. The manufacturing of grade A dry milk is compliant with all requirements to which it is manufactured within the state of Pennsylvania and follows the requirements of the PMO. BlendHouse's quality assurance lab is "under a program of routine laboratory control which has been checked by the State laboratory approval agency," requiring us to be screened biannually by the Laboratory Evaluation Officer. We are audited by the PDA on the milk itself, what farms it comes from, and if that farm is listed on the Interstate Milk Shippers (IMS), if we meet proper pasteurization time and temperature, and if we complete accurately Appendix N testing (antibiotic) of incoming milk. Both scorched particles and solubility are evaluated during manufacturing and results are reported per production for internal information only as these tests are not a condition of compliance for dry whole milk in the state of Pennsylvania. ByHeart's internal solubility test provides "pass/fail" results. All data to date have been reported as "pass" under this method. Secondarily, we test our grade A dry milk at Eurofins for Nitrogen Solubility Index (NSI; ISO 15323:2002) because this method is widely available in laboratories in the US. Data reported at time of manufacture for NSI for the 3 lots of the grade A dry milk as part of our stability program were 77%, 78.9%, and 79.7% respectively (Tables 3 & 4 of notice). These values for NSI are within the expected ranges (70%-90%) for milk protein powders. In consultation with Darryl Sullivan, Chief Science Officer– Eurofins, the NSI method scope has been extended to dairy products, where it has been used successfully for the evaluation of dispersibility and solubility of protein.

Per OFAS request to add the specification for Solubility Index (SI) as given in the USDA Standards to Table 2 of the Notice and include at least three non-consecutive batch analyses, we will be implementing this SI method at our manufacturing site prior to commercial use in addition to our current protocol; the method has been developed and equipment identified to conduct this testing.

Additionally, our manufacturing site tests scorched particles (USDA 918-RL; ADPI) and results reported were <7.5mg- ADPI Disc A. Table 2 has been revised to include this specification and related results. See updated Table 2 in the response to Q7.

10. P.6 of the notice (2.1. Name of the GRAS Substance) includes a statement that according to 21 CFR 131.147, dry whole milk contains not less than 26% but less than 40% by weight of milkfat; however, the specification for the fat content of the notified substance in Table 2 only includes a lower limit of 26%. Please clarify this discrepancy.

Response:
An upper specification for fat has been added consistent with 21 CFR 131.147. See updated Table 2 in the response to Q7.

11. The specification listed in Table 2 for protein content of dry whole milk is not less than 18.7% and the results of batch analysis indicate a content of approximately 25%. Please discuss the upper limit for protein content.

Response:
Based on the consistency of the analytical data for the lots tested, we have revised the specification with an acceptable range for protein between 22-30%. See updated Table 2 in the response to Q7.

12. Please confirm that the cited methodologies for specification parameters are the most recent and validated for the test article. For many of the specifications listed in the notice, multiple methods are cited, which have differing conditions or applicability.
    - The methods listed for moisture determination are AOAC 925.09 (Moisture of Flour) and 926.08 (Moisture of Cheese). We note AOAC 927.05 (Moisture in Dried Milk) may be a more appropriate alternative.
    - The methods listed for protein determination are AOAC 968.06 (Protein (Crude) in Animal Feed) and 992.15 (Crude Protein in Meat and Meat Products Including Pet Foods). We note possible alternatives that may be more appropriate, including: AOAC 975.17 (Protein in Milk), AOAC 2016.15 (Quantification of Whey Protein Content in Milk-Based Infant Formula Powders).
    - The method listed for ash determination is AOAC 923.03 (Ash of Flour). We note possible alternatives that may be more appropriate, including: AOAC 945.46 (Ash of Milk) or AOAC 930.30 (Ash of dried milk).
    - The methods listed for determination of iron, sodium, and potassium include AOAC 984.27 (Calcium, Copper, Iron, Magnesium, Manganese, Phosphorus, Potassium, Sodium, and Zinc in Infant Formula), AOAC 985.01 (Metals and Other Elements in Plants and Pet Foods), and AOAC 2011.14 (Ca, Cu, Fe, Mg, Mn, K, P, Na, and Zn in Fortified Food Products). We note method AOAC 985.01 does not include iron or sodium, and that a possible alternative that may be more appropriate would be AOAC 2015.06 (Minerals and Trace Elements in Milk, Milk Products, Infant Formula, and Adult/Pediatric Nutritional Formula).
    - The methods listed for determination of chloride include AOAC 963.05 (Chlorides in Tobacco), AOAC 971.27 (Sodium Chloride in Canned Vegetables), and AOAC 986.26 (Chloride in Milk-Based Infant Formula). We note a possible alternative that may be more appropriate to be AOAC 2016.03 (Chloride in Milk, Milk Powder, Whey Powder, Infant Formula, and Adult Nutritionals).
    - The methods listed for determination of heavy metals include AOAC 993.14 (Trace Elements in Waters and Wastewaters) and AOAC 2011.19 (Chromium, Selenium, and Molybdenum in Infant Formula and Adult Nutritional Products). The older method does not include mercury and the latter method is specifically for determination of chromium, selenium, and molybdenum. We note possible alternatives that may be more appropriate, including AOAC 2013.06 (Arsenic, Cadmium, Mercury, and Lead in Foods) and AOAC 2015.01 (Heavy metals in food), which includes infant formula but does not include mercury as an analyte.

Response:

We are submitting separately a signed response written by Mr. Darryl Sullivan, Chief Science Officer at Eurofins Scientific. Mr. Sullivan has confirmed the acceptability of the test methods cited in the notice that were used by Eurofins for dry whole milk. Mr. Sullivan has more than 40 years of experience in the food industry as a scientist, laboratory director, and business executive, and leads research and development teams to develop and validate test methods for infant formula, nutritional products, and dietary supplements.

13. The citations for the AOAC methods used for detection of microbial contaminants are not provided. Please provide those citations.

Response:
As requested, the citations for the AOAC methods used for detection of microbial contaminants are provided here. These methods are also in updated Table 2 in the response to Q7.

- Microbiological --- AOAC / BAM Method citation(s)
- Coliforms --- CMMEF Chapter 8.7
- Mold --- FDA BAM Chapter 18 mod.
- Yeast --- FDA BAM Chapter 18 mod.
- *B. cereus* --- FDA BAM Chapter 14
- Enterobacteriaceae --- CMMEF Chapter 9.62
- *S. aureus* --- BAM Chapter 12
- *Listeria* spp. --- BAX PCR detection, method AOAC-RI 050903
  Cultural Confirmation - *Listeria* spp per BAM Chapter 10
- *Salmonella* LAMP detection --- AOAC 2016.01
- *Cronobacter* species D --- BAX® System PCR Assay for *E. sakazakii (Cronobacter)*
  Cultural Confirmation - *Cronobacter* spp. per BAM Chapter 29

14. The method cited for determination of *Salmonella* (AOAC 091501) does not appear to be a valid method number. Please clarify.

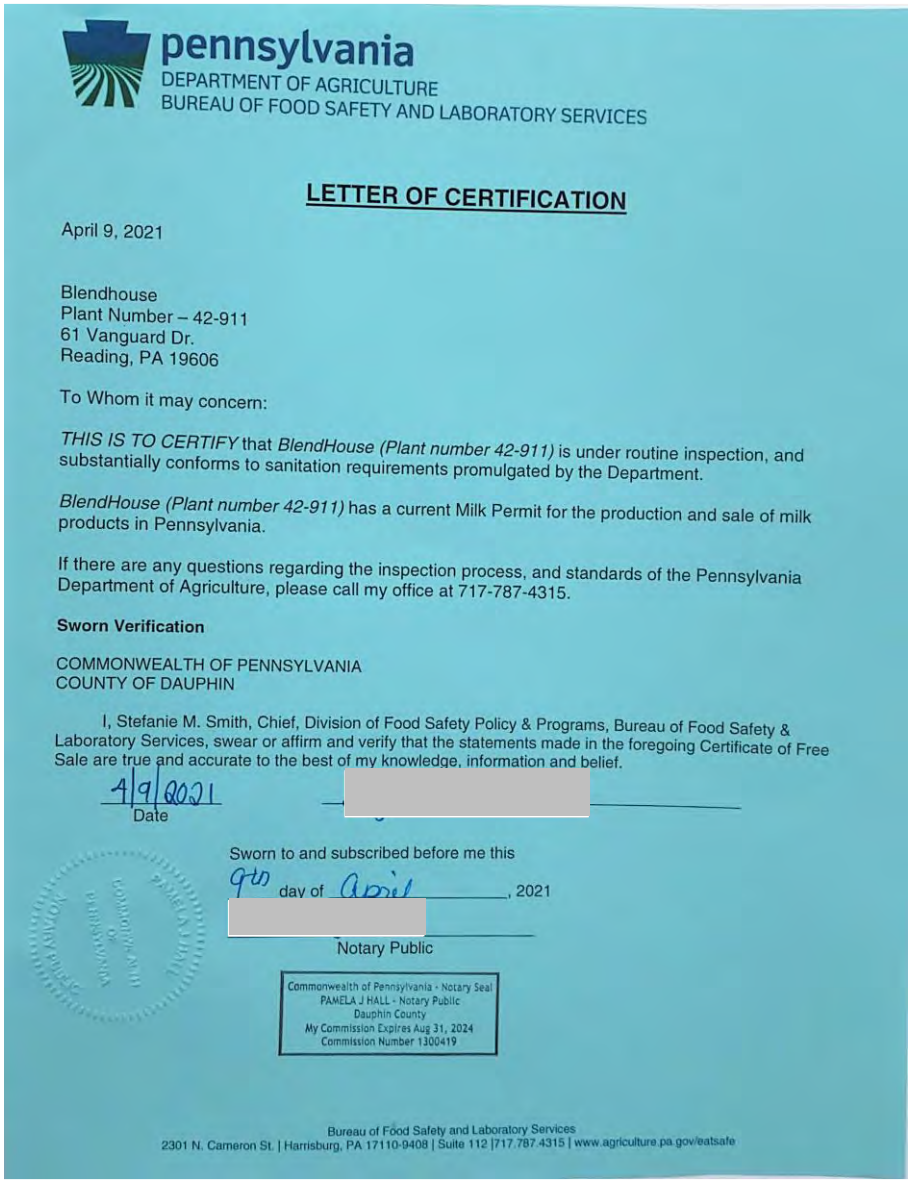
Response:
Eurofins has confirmed that the correct method for determination of *Salmonella* is AOAC 2016.01. This method is also updated in updated Table 2 in the response to Q7.

15. The method cited for determination of iodide (AOAC 2212.15) is not currently a valid method number. We note that this may be a typographic error and the intended method was AOAC 2012.15 (Total Iodine in Infant Formula and Adult/Pediatric Nutritional Formula). Please clarify if this is correct.

Response:
We confirm that the correct method for the determination of iodide is AOAC 2212.15, not the method cited in the notice (AOAC 2012.15); this was a typographical error. This method is also in updated Table 2 in the response to Q7.

16. Food-grade milk products are produced in compliance with 21 CFR 1240.61 (mandatory pasteurization for all milk and milk products in final package form intended for direct human consumption). Although Figure 1 on p. 9 of the notice (i.e., Process Flow Diagram of ByHeart's Dry Whole Milk) includes a step labeled as "pasteurizer," we request confirmation that the milk used in the manufacture of dry whole milk is pasteurized in accordance with the provisions of the Pasteurized Milk Ordinance (PMO).[2] The PMO is the milk sanitation standard for Grade "A" milk and milk products used by the National Conference on Interstate Milk Shipments program.

Response:
BlendHouse is certified as a milk handler and is inspected and sealed by the Pennsylvania Department of Agriculture. For each production, the Pennsylvania Department of Agriculture is onsite, and the milk used in the manufacture of Grade "A" dry whole milk is considered pasteurized in accordance with the provisions of the Pasteurized Milk Ordinance (PMO). A letter of certification from the Pennsylvania Department of Agriculture is shown below.



pennsylvania
DEPARTMENT OF AGRICULTURE
BUREAU OF FOOD SAFETY AND LABORATORY SERVICES

LETTER OF CERTIFICATION

April 9, 2021

Blendhouse
Plant Number – 42-911
61 Vanguard Dr.
Reading, PA 19606

To Whom it may concern:

THIS IS TO CERTIFY that *BlendHouse (Plant number 42-911)* is under routine inspection, and substantially conforms to sanitation requirements promulgated by the Department.

BlendHouse (Plant number 42-911) has a current Milk Permit for the production and sale of milk products in Pennsylvania.

If there are any questions regarding the inspection process, and standards of the Pennsylvania Department of Agriculture, please call my office at 717-787-4315.

Sworn Verification

COMMONWEALTH OF PENNSYLVANIA
COUNTY OF DAUPHIN

I, Stefanie M. Smith, Chief, Division of Food Safety Policy & Programs, Bureau of Food Safety & Laboratory Services, swear or affirm and verify that the statements made in the foregoing Certificate of Free Sale are true and accurate to the best of my knowledge, information and belief.

4/9/2021
Date

Sworn to and subscribed before me this
9th day of April, 2021

Notary Public

Commonwealth of Pennsylvania - Notary Seal
PAMELA J HALL - Notary Public
Dauphin County
My Commission Expires Aug 31, 2024
Commission Number 1300419

Bureau of Food Safety and Laboratory Services
2301 N. Cameron St. | Harrisburg, PA 17110-9408 | Suite 112 |717.787.4315 | www.agriculture.pa.gov/eatsafe

17. Please note that standards and regulations for environmental contaminants, animal drugs, and pesticides in foods such as milk are outlined in 21 CFR 109.30 (tolerances for PCBs), 21 CFR Part 556 (tolerances for residues of new animal drugs in food), and 40 CFR Part 180 (tolerances for pesticides in food and feed). FDA also has action levels for several pesticides (listed in Compliance Policy Guide (CPG) 575.100) and for aflatoxin M1 (CPG Section 527.400). In addition to tolerances and action levels, FDA also may use "target testing levels" as guidelines for certain drug residues, including those with a tolerance of zero in milk (e.g., erythromycin, penicillin). In accordance with Appendix N of the PMO, target testing levels have been communicated via Memoranda of Information (M-I) from FDA, most recently M-I-18-9, issued February 12, 2018.3 Please discuss the potential presence of persistent environmental contaminants (i.e., dioxins, furans, PCBs, pesticides) and radioactivity (Cs-134/137) to support the safety of the dry whole milk and demonstrate that the regulatory limits are met. In particular, please confirm the following:

- The starting material for dry whole milk is produced in accordance with good agricultural practices and meets applicable U.S. regulations.
- The starting material for dry whole milk complies with derived intervention levels for radionuclides (CPG 560.750).
- The starting material for dry whole milk meets pesticide tolerances specified in 40 CFR Part 180 for milk and milk fat.
- The starting material for dry whole milk meets U.S. regulatory limits for veterinary drug residues in milk and milk fat, and pesticides, and is tested regularly for contaminants as outlined in the Grade "A" PMO (2019).

Response:

Our supplier confirms that the grass-fed organic milk is produced according to all applicable standards and certification requirements for raw (liquid) milk. This attestation is provided to FDA as a separate attachment, redacted to keep our supplier information confidential.

For radionuclides, CPG 560.750 has since been rescinded and replaced by CPG 550.880[4]. ByHeart sources its raw milk from local US farms that are not located near a nuclear or nuclear waste facility. After RO treatment, our local water supply is tested annually, including testing for radionuclides. Nonetheless, our raw milk supplier, US based and not subject to import, affirms in their letter that the raw milk is sourced from local farms that are not located near nuclear or nuclear waste facilities.

[4] CPG Sec 555.880 Radionuclides in Imported Foods - Levels of Concern | FDA

18. As noted in question 2, the intended use of ByHeart's dry whole milk is unclear.
    - Please indicate how ByHeart intends to use dry whole milk as a source of protein: for example, will it be used as a sole source of protein for infant formula or will it be supplemented with other proteins?
    - Since ByHeart's ingredient contains many substances other than protein, such as fats and phospholipids, please clarify whether other components in the article of commerce will serve as a sole source of other nutrients (such as fats) or be supplemented by additional relevant nutrients.

Response:

The dry whole milk is not the sole source of protein in the infant formula. The protein contributed by the dry whole milk, when added at maximum use level of 16g/100g infant formula powder, is approximately 26% of the formula protein. The predominant balance of the formula protein comes from added whey ingredients.

The dry whole milk is not the sole source of fat for the infant formula. The fat contributed by the dry whole milk, when added at maximum use level of 16g/100g infant formula powder, is approximately 12% of the formula fat. The predominant balance of the formula fat comes from added vegetable oils and long chain omega-3 and 6 fatty acids (DHA and ARA).

The addition of dry whole milk in the ByHeart formula also contributes a small portion of lactose and some vitamins and minerals, with the predominant balance coming from other sources.

The ByHeart infant formula containing dry whole milk at the maximum use level of 16g/100g infant formula powder meets all nutrient specifications for infant formula as given in 21CFR107.100.

19. Because the safety narrative in the notice almost entirely rests on the safety of cow milk in infants, how cow milk as consumed in its entirety as a sole source of nutrition compares to ByHeart's article of commerce as used in the context of infant formula would be an important component of a safety assessment. In section 6.4. Studies in Infants and Toddlers, ByHeart concludes that none of the 23 studies found in the literature in which whole milk was given to infants or toddlers showed "adverse events attributable to feeding of whole milk reported other than iron deficiency among children not receiving iron fortification or supplementation."

- We note that Table 9 does not provide specific ages of the infants for many of the studies. Furthermore, we note that many of the cited studies involve the use of whole milk that is fortified with iron and vitamin C and/or mixed with foods (noodles, vegetables, etc.)—thus, there appears to be no studies involving infant formula fed as the sole source of nutrition that contained whole milk as an ingredient. Please provide a narrative clarifying how these cited studies support the safe use of ByHeart's ingredient.
- ByHeart did not cite and discuss Ziegler (2011),4 which states:

  "Although these reports demonstrate that iron fortification of CM [cow milk] is associated with better iron nutritional status than unfortified CM, it remains unclear whether fortification completely offsets the adverse effects of CM. One variable that seems crucial in this regard is the amount of iron added to the milk." (emphasis added)

  In addition to CM's low iron levels, a number of components of CM (i.e., casein and calcium) may strongly inhibit iron absorption (also discussed in Fomon (2001), which is cited in the notice). Please discuss the impact of iron bioavailability of cow milk and how this potential safety concern will be addressed or mitigated by the intended use.
- Ziegler (2011) also discusses potential adverse effects of cow milk due to its high protein and electrolyte content, leading to higher potential renal solute load. Given the intended use as a "source of protein", please discuss how this potential concern will be mitigated by the intended use.
- Fomon (1993) reports that cow milk butterfat is poorly absorbed by infants; yet the notice does not discuss whether or not ByHeart's intended use "as a component of non-exempt infant formula" can ensure adequate fat absorption by infants. Please provide a narrative describing why this is not a safety concern.

Response:

[FIRST BULLET]

The revised copy of Table 9, shown on the following pages, includes all information available in the published studies regarding the specific ages of the infants and toddlers (all added information is in red).

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Alarcon et al. 1991	Prospective, randomized, multi-arm trial of the treatment of acute childhood diarrhea	85 Peruvian infants and children aged 5-24 months (stratified into ages 5-6 months and 7-24 months; mean age = 11.9±4.2 months) hospitalized for acute diarrhea	110 kcal/kg bw/day from: 1) Dried whole milk, potato flour, carrot flour, sucrose & veg oil 2) Wheat flour, pea flour, carrot flour, sucrose, & veg oil 3) Soy-protein isolate lactose-free formula	Children in all groups gained weight with no differences in anthropometric status, energy intakes, energy absorption, nitrogen retention, or fecal output and no differences in treatment failure. The authors concluded that "these locally available, low-cost staple food mixtures [i.e., interventions 1 and 2] offer a safe and nutritionally adequate alternative to a commercially produced lactose-free formula for the dietary management of young children with acute diarrhea in this setting."
Bonuck et al. 2014	Observational cohort study of dietary intake and overweight at 12 months of age	286 low-income infants and toddlers aged 12.6±0.5 months (186 normal, 100 overweight)	Measurements of dietary intake, anthropometrics, meal-time behavior	Normal weight and overweight toddlers did not differ in consumption of whole milk, mean daily energy intake, intake of fat, saturated fat, or protein. The total sample consumed a mean of 2.0±1.8 cups of whole milk per day. Whole milk consumption was lower in overweight vs. normal weight toddlers (1.7±1.8 vs. 2.1±1.8 cups/day). Thus, consumption of whole milk was not associated with overweight.
Brown et al. 1991	Prospective, randomized, double-blind, placebo-controlled trial of the management of acute childhood diarrhea	116 Peruvian male infants and toddlers aged 3-24 months (mean age = 12.5±6.1 months) with acute diarrhea	55 to 110 kcal/kg bw/day from: 1) Whole milk & wheat noodles 2) Lactose-hydrolyzed whole milk & wheat noodles 3) Modified whole milk 4) Lactose-hydrolyzed milk formula	The combination of milk and noodles resulted in reduced stool outputs, shorter durations of diarrhea, and lower rates of treatment failure than did milk alone. The authors concluded that "the noodle-milk diets employed during this study were safer than the milk diets for the dietary management of children with acute diarrhea."
Fomon et al. 1981	Prospective, randomized, placebo-controlled trial of whole-milk feeding in infancy	81 normal healthy infants aged 112 days	Given pasteurized whole milk (n = 39) or Enfamil (n = 42) for 12 weeks	Incidence of blood in stool was greater among infants fed whole milk from age 112 to 140 days; no difference thereafter. [N.B. No iron supplementation was provided.] No difference in mean hemoglobin, hematocrit, serum iron, total iron-binding capacity, or transferrin saturation.

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Hertramph et al 1990	Prospective, randomized, placebo-controlled trial of fortification to prevent iron-deficiency	190 healthy infants enrolled at 3 months of age and followed for 6 months	84 infants received whole milk supplemented with 15 mg ferrous sulfate & 100 mg ascorbic acid/100 g powder; 104 infants received the same milk with no supplement for 9 months	All iron nutritional parameters were higher in the supplemented group. Iron-deficiency anemia was reported in 34% of the control but 0% of the treatment group. The authors concluded that, "The product exhibited excellent tolerance and could therefore be used to eradicate iron-deficiency anemia of the infant."
Hjelt et al 1989	Prospective, randomized, placebo-controlled trial of refeeding in acute pediatric gastroenteritis	52 infants and children aged 6-46 months (mean age = 17 months) hospitalized with acute gastro-enteritis after oral rehydration	Subjected to either rapid refeeding (lactose-treated whole milk as only fluid intake; n = 27) or gradual refeeding (fluids other than whole milk; n = 25) for 7 days	The two regimens produced similar results with regard to duration and severity of diarrhea and vomiting. The rapid-refeeding group derived more energy from fat and protein and less from carbohydrate than did the gradual-refeeding group. Milk provided 47-59% of the daily energy intake of the rapid-refeeding group. The authors reported that the whole milk was well accepted and no signs of cow's milk protein intolerance were observed. They suggested that the milk-based rapid-refeeding regimen can be employed "without the fear of negative effects on the outcome."
Houghton et al. 2011	Prospective, randomized, single-blind, placebo-controlled trial of vitamin D-fortified whole milk & 25-hydroxy-vitamin D level	181 healthy toddlers aged 12-20 months (mean age 17 months)	Toddlers received red meat or vitamin D-fortified whole milk for 20 weeks.	After 20 weeks, serum 25(OH)D concentrations but not parathyroid hormone were significantly raised in the milk group. The prevalence of having a serum 25(OH)D <50 nmol/L remained unchanged at 43% in the meat group, whereas it decreased to between 11 and 15% in those consuming fortified whole milk. The authors concluded that "habitual consumption of vitamin D-fortified milk providing a mean intake of nearly 4 μg/d was effective in achieving adequate year-round serum 25(OH)D for most children."
Isolauri et al. 1986	Prospective, randomized, placebo-controlled trial of refeeding in acute pediatric gastroenteritis	65 infants and toddlers (aged 14.7±7.2 months) hospitalized for acute gastro-enteritis	Refeeding included whole milk (n = 38) or no milk (n = 27)	The authors reported that, "There was no difference between the groups in the clinical recovery from diarrhea. No child had prolonged diarrhea. No new cases of clinical atopy were observed at 1-month follow-up, and there were no significant increases in the total or milk-specific IgE levels. Serum IgG and IgA antibodies to β-lactoglobulin and α-casein were initially present in the majority of the children, but there were no appreciable changes in these cow's milk antibodies after gastroenteritis regardless of the type of diet. It is concluded that cow milk and milk products can be safety given in acute gastroenteritis as parts of the mixed diet for children over 6 months of age."

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Lamkjaer et al. 2009	Prospective, randomized, placebo-controlled trial of whole milk v. infant formula on growth and IgF-I	83 healthy infants with a mean age of 9.1±0.3 months, followed to age 12.1±0.3 months	In a 2x2 design, infants received whole milk or infant formula, with or without fish oil	Intake of whole milk significantly increased protein energy percentage and serum urea nitrogen; there was no effect on anthropometric measures of growth. The whole-milk intervention increased IGF-I in boys but not in girls. Intake of fish oil had no effect on the outcomes. The authors concluded that, "Randomization to whole milk had no overall effect on growth. However, the positive effect of whole milk on IGF-I in boys and the positive association between protein energy percentage and IGF-I at 9 and 12 months is consistent with the hypothesis that a high milk intake stimulates growth."
Maulen-Radovan et al. 1999	Prospective longitudinal study of the impact of fortified whole milk in children	227 generally healthy infants and children aged 8-60 months (93 aged 8-24 months [15,5±4.9 mo]; 70 aged 25-41 months [32.47±4.2 mo]; 64 aged 42-60 months [48.85±5.1 mo]); included 45 malnourished & 36 anemic children	Toddlers and children consumed 500 ml fortified whole milk/day for 90 days	"The milk was well tolerated and widely accepted." Anthropometric measures, hemoglobin, serum iron, vitamin B12, and folic acid all increased. The authors concluded, "The consumption of a fortified whole milk during 90 days improved significantly the nutritional status of the children, the weight for height Z score, the plasma level of vitamin B12 and Hb, and decreased the number of anemic and malnourished children."
Penrod et al. 1990	Retrospective cohort study of infant formula vs. cow's milk in infancy	100 infants and toddlers aged 45.6±1.0 weeks	55 infants had been receiving infant formula for at least 3 months prior to enrollment; 45 infants had been receiving whole cow's milk	The infants receiving the fortified infant formula had significantly better iron status than those receiving whole milk and lower weight. [N.B. No iron supplementation was provided.] The two groups did not differ in other measures of nutritional status. The authors noted that some differences may result from differences in beikost rather than primary beverage.

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Stekel et al. 1986	Mono-and double-isotopic analysis of iron absorption by infants consuming different types of cows' milk formulas	364 infants and toddlers aged 5-18 months	Following an overnight fast, formulas containing $^{59}FeSO_4$ were fed by bottle; infants consumed 100-250 ml in a single bolus dose of one of 7 types of lowfat milk or one of 4 types of whole milk and iron absorption was measured	There was no significant difference in absorption of iron from the milk or from ferrous sulfate supplementation due to the level of milk fat. Iron absorption ranged from 2.9 to 5.1%, with no correlation with the milkfat content. These findings indicate that use of whole milk rather than lowfat milk in infant formula does not interfere with the absorption of iron from the formula.
Stekel et al. 1988.	Prospective, randomized, placebo-controlled trial of supplemented vs. unsupplemented whole milk	554 infants with birthweight >2500 g	276 infants received whole milk supplemented with ferrous sulfate & ascorbic acid for 12 months	The authors reported that, "the acceptability of this milk was excellent." 2.5% of infants in the group receiving whole milk + supplements had iron deficiency anemia compared with 25.7% of the control group.
Svahn et al. 2000	Prospective, randomized, placebo-controlled trial of the effect of quantity and quality of fat	38 healthy infants and toddlers aged 12 months	Fed one of 4 milks for 6 months: 1) lowfat cow's milk 2) whole cow's milk 3) partially veg. fat milk 4) wholly veg. fat milk	There was a lower percentage of saturated fatty acids in plasma triacylglycerol in toddlers fed low-fat milk or milk with 50% or 100% vegetable fat than in children fed whole milk. Plasma polyunsaturated fatty acid levels were significantly higher in children fed milk with vegetable fat than in children fed whole milk. Blood lipid concentrations were lower in children fed milk with 50% vegetable fat. No adverse events were reported.
Thomas et al. 1986	Longitudinal cohort study of infant feeding and excretion of hemoglobin and α_1-antitrypsin (FA1AT)	820 healthy infants aged 2 weeks to 12 months stratified by age: 2-8 wk, 9-16 wk, 17-25 wk, 26-33 wk, 34-42 wk, 43-52 wk	Infants were receiving: 1) whole milk (n = 146) 2) breast milk (n = 354) 3) infant formula (n = 320)	Levels of fecal hemoglobin and FA1AT were low in all groups and showed little difference by type of feeding. The authors reported that, "unrecognized intestinal abnormalities, as based on hemoglobin and FA1AT excretion, appear to be uncommon in healthy infants fed a balanced diet and fresh cow's milk. Human milk-fed infants had higher FA1AT concentrations than infants receiving formula or cow's milk. However, total daily FA1AT excretion was similar in all three milk-feeding groups. The differences in FA1AT concentration were a function of differences in daily stool output in response to diet." They concluded, "our data support the recent recommendation of the

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
				Committee on Nutrition of the American Academy of Pediatrics to allow introduction of pasteurized, fresh whole cow's milk into the diets of infants older than 6 months of age."
Torres et al. 1995	Longitudinal open-label study of iron-fortified whole milk and toddler's nutritional status	335 toddlers <2 years of age	Toddlers consumed dry whole milk fortified with 9 mg iron & 65 mg vitamin C/100 g for 6 months	Average hemoglobin increased from 10.4 to 11.6 g/dl. No intervention-associated adverse events were reported and the authors concluded that, "the utilization of enriched foods is an excellent alternative in the treatment of iron deficiency in populations of children under 2 years of age."
van der Gaag and Forbes 2014	Case-controlled retrospective study of a high-fat diet in children with non-specific elevated IgE	105 children aged 1-18 years (median age = 4.65 years) with non-specific elevated IgE	49 children were encouraged to consume at least 200 ml whole milk/day, beef, butter, and green vegetables, while 56 were not. Children were followed for 1 year.	The intervention group demonstrated a greater decrease in IgE (9.2 vs. 0.1 kU/L) and were more likely to report improvement in symptoms (53.2% vs. 28.6%). The authors concluded that, "Overall, the effects of nutrients and vitamins on the decrease in IgE are promising." They did not report any intervention-associated adverse events.
van der Gaag et al. 2017	Retrospective cohort study of a high-saturated-fat diet in children	121 children aged 1-16 years (median age = 3.6 years)	All children received dietary advice to consume whole milk, beef, butter, and green vegetables. 55 of them adhered to the advice, while 66 did not. Measures were taken over 3 months	In the group following the advice to consume a diet high in saturated fat, including whole milk, there was a significant reduction in the cholesterol/HDL ratio and non-HDL-cholesterol and an increase in HDL-cholesterol, while there was no difference in the BMI and BMI z-scores. The authors reported that, "The dietary advice has no adverse effect on the lipid profile, BMI, and BMI z-scores in children, but has a significant beneficial effect on the cholesterol/HDL ratio, non-HDL-cholesterol, and the HDL-cholesterol," and concluded, "The dietary advice can, therefore, be safely recommended and might be beneficial for children with recurrent respiratory tract infections."
van der Gaag et al. 2020	Prospective, randomized, controlled trial of a high-saturated-fat diet in pediatric upper respiratory tract infections	118 toddlers aged 1-4 years (mean age = 2.4±1.1 years) with recurrent upper respiratory tract infections	58 children were encouraged to consume at least 300 ml whole milk/day, beef, butter, and green vegetables, while 60 were not. Children were followed for 6 months.	Children in the dietary advice group had a mean of 4.8 days per month with symptoms of an upper respiratory tract infection in the last three months of the study, compared to 7.7 in the control group. The use of antibiotics was significantly reduced in the dietary advice group. No adverse events were reported. The authors suggested that "this diet provides parents with a tool to improve the health of their children."

Table 1. Published Research on Bovine Whole Milk.

Reference	Study Design and Objective	Subjects	Intervention and Duration	Safety-Related Results
Vanderhout et al. (2016a)	Cross-sectional analysis of milk-fat percentage and BMI in early childhood	2745 healthy urban toddlers and children aged 12-72 months (mean age = 34.9±16.6 months)	Adjusted bivariate linear regression of milk-fat percentage and BMI z-score and 25-hydroxyvitamin D status	Children who drank whole milk had a 5.4-nmol/L higher median 25(OH)D concentration and a 0.72 lower BMI z-score than children who drank 1% milk. The authors concluded that, "Whole milk consumption among healthy young children was associated with higher vitamin D stores and lower BMI."
Vanderhout et al. (2016b)	Cross-sectional analysis of milk-fat percentage and 25-hydroxyvitamin D in childhood	2857 healthy urban toddlers and children aged 12-72 months (mean age = 33.7±16.6 months)	Adjusted multivariate linear regression of milk-fat percentage and milk volume and 25-hydroxyvitamin D status	Children who drank 1% milk needed 2.46 cups of milk to have the 25(OH)D status of children who drank 1 cup of whole milk. Children who consumed 1% milk had 2x higher odds of having a 25(OH)D concentration <50 nmol/L than children who consumed whole milk. The authors concluded that "recommendations for children to drink lower-fat milk (1% or 2%) may compromise serum 25(OH)D levels and may require study to ensure optimal childhood health."
Wong et al. 2019	Longitudinal study of milk fat intake and non-HDL in young children	2890 children aged 2-8 years (mean age = 46.0±18.7 months)	Statistical analyses of the relationship between cow's milkfat intake and serum non-HDL cholesterol concentration	There was a small positive correlation between milkfat intake and non-HDL cholesterol, but not with the odds of having high non-HDL cholesterol. The authors concluded that the correlation exists, but with no indication of leading to high non-HDL cholesterol.
Ziegler et al. 1990	Prospective, randomized, placebo-controlled trial of infant feeding and GI blood loss	52 healthy term infants aged 24 weeks	26 infants each were assigned to receive whole cow's milk or infant formula for 12 weeks.	There were no differences between groups in parental reports of regurgitation, vomiting, constipation, or other feeding-related behavior. Stool hemoglobin concentration increased with the introduction of whole cow milk from 622±527 µg/g dry stool at baseline to 3598± 10,479 µg/g dry stool during the first 28 days of Ingestion of whole cow milk. Among infants fed formula, stool hemoglobin did not Increase and was significantly less than in the whole milk group. Stools with occult blood increased from 3.0% at baseline to 30.3% in the whole-milk group during the first 28 days of the trial, whereas the proportion of positive stools remained low (5.0%) with the feeding of formula. The proportion of occult-blood-positive stools among whole-milk-fed infants declined later, but for the entire trial it remained significantly elevated. The authors concluded that, "a large proportion of normal nonanemic infants respond to the feeding of pasteurized cow milk [i.e., whole milk as the sole source of nutrition and no added iron] with increased fecal loss of blood."

[FIRST BULLET]
FDA states that "there appears to be no studies involving infant formula fed as the sole source of nutrition that contained whole milk as an ingredient." Actually, there are several cited studies of infant formulas containing whole milk that were fed as the sole source of nutrition. FDA probably means that there are no studies in which whole milk, unfortified, was fed as the sole source of nutrition. This is correct.

To the best of our knowledge, after a thorough review of the published literature, there are no published studies involving infant formula with whole milk as the sole ingredient. If the point of this literature review were to appraise the efficacy of dry whole milk in infant formula, and its ability to support normal growth absent any other components such as iron or vitamin C fortification, then this literature would fail to do so. But, in our opinion, this literature review does succeed in demonstrating that dry whole milk is safe as a component of the infant diet. If whole milk powder were not safe, adding iron or vitamin C, or mixing it with noodles, would not render it safe. The point of the literature review was to determine that no adverse effects result from ingestion by infants or toddlers of whole milk as an ingredient in infant formula.

Dry whole milk is intended by ByHeart for use simply as one ingredient of infant formula. Like other ingredients of infant formula, it is not expected to serve as the sole source of nutrition. It is, however, expected to be safe as a component of infant formula, and—in our opinion—the studies cited in Table 9 support the conclusion of the GRAS Expert Panel that it is safe for that intended use.

[SECOND BULLET]
As noted by FDA, Ziegler (2011) addresses the issue of poor iron status among infants and toddlers consuming cow's milk alone or in infant formula with inadequate iron fortification. He states that "formulas that have iron concentrations between 6 and 12 mg/L easily meet infants' iron needs." Ziegler attributes the poor iron status of infants receiving cow's milk as their sole source of nutrition primarily to its low iron content but suggests that the problem may be exacerbated by the presence of casein and calcium, inhibitors of iron absorption.

We feel it is clear that when Ziegler speaks of cow's milk, he is thinking of whole milk, not nonfat milk, simply because the unsuitability of nonfat milk as a sole source of infant nutrition is self-evident. We believe it is equally obvious that all the concerns expressed regarding the use of whole milk as a sole source of infant nutrition would apply as well to nonfat milk—it is just as low in iron content and just as high in casein and calcium as is whole milk. But the unsuitability of nonfat milk as a sole source of infant nutrition clearly does not impugn its safety as an ingredient in infant formula, and it is far from clear why whole milk should be regarded differently.

Our opinion (shared by our Expert Panel) is that, while whole milk (like nonfat milk) cannot function as a sole source of nutrition for infants, this in no way indicates that whole milk (like nonfat milk) is not safe as a component in a properly formulated infant formula.

[THIRD BULLET]
This same rationale applies to Ziegler's discussion of adverse effects of cow's milk due to its high protein and electrolyte content: it is not clear to us why the protein and electrolyte content of whole milk, which is similar to that of nonfat milk, should uniquely pose a risk that nonfat milk does not.

[FOURTH BULLET]
The percent of total formula calories contributed by butterfat in the ByHeart formula is 6%, and the percent of total fat calories contributed by butterfat in the ByHeart formula is 12%. Butterfat in the formula derives solely from the dry whole milk addition; it was never meant to be the sole source of formula fat. Vegetable oils make up the balance of fat calories (88%) in the ByHeart formula.

ByHeart has tested the total fatty acids in the ByHeart formula, and their profile and amount are not unlike those in tested current U.S. infant formulas. This difference -- 88% vs 100% -- of total fat calories coming from vegetable oils is not a large one, and there is no reason to believe that the small portion of butterfat in the ByHeart formula would be unsafe or even less absorbed than in vegetable oils.

Regarding absorption, a larger portion of C16 fatty acids from butterfat exist preferentially in the sn-2 position on the triglyceride than do the C16 fatty acids from vegetable oils, where they are more equally distributed along the triglyceride backbone[5]. As the sn-2 positioning positively affects absorption, the expectation would be that the C16 fatty acids from butterfat would be better absorbed than the C16 fatty acids from vegetable oils. The fatty acids from vegetable oils during digestion would be cleaved from the 1 and 3 positions, resulting in a greater tendency to form calcium soaps, whereas than the fatty acids from butterfat, with C16 fatty acids being more predominant in the sn-2 position, would have less of a tendency to form calcium soaps because they would still be tied up in the sn-2 position of the triglyceride backbone[5].

[5] Hageman JHJ, M Danielsen, AG Nieuwenhuizen, AL Feitsma, TK Dalsgaard. 2019. Comparison of bovine milk fat and vegetable fat for infant formula: Implications for infant health. *Int Dairy J* 92:37-49

20. In Table 9, ByHeart indicates that the Thomas et al., 1986 study concluded "our data support the recent recommendation of the Committee on Nutrition of the American Academy of Pediatrics to allow introduction of pasteurized, fresh whole cow's milk into the diets of infants older than 6 months of age." OFAS notes, however, that AAP subsequently changed this recommendation for those not able to breastfeed to feed infant formula for one year to reduce risk of iron-deficiency anemia. Please clarify this discrepancy.

Response:

The American Academy of Pediatrics recommends that infants be fed breast milk or, as an alternative, fed an iron-fortified infant formula up to the first year of life. Whole cow's milk and low-iron formulas are not recommended to be used as sole sources of nutrition during this time. The 1992 recommendation not to use whole cow's milk as a sole source of nutrition is consistent with the previous statement, that, if fed in place of breast milk or iron-fortified formula, feeding of unsupplemented cow's milk could raise the risk of iron-deficiency anemia (if consumed at 35% to 100% of total daily calories). ByHeart's dry whole milk is not intended to be used as a sole source of nutrition; it is used as a component of infant formula and this intended use is fully consistent with AAP's current recommendations.

21. In question 2, it is unclear what is meant by ByHeart's statement on p. 13 "to provide nutrients more closely resembling those found in breast milk." How does using bovine whole milk as an ingredient in infant formula make the formula more like human milk?

Response:

We agree that in the context of the safety assessment regarding the use of dry whole milk, the intended use of the ingredient should be consistent across the notice.

We clarify that the dry whole milk is intended as an ingredient in ByHeart's whey-based, non-exempt infant formula to be fed as a sole source of nutrition from the first day of life in healthy term infants.

To that end, we amend the paragraph on page 13 as follows:

> *Dry whole milk powder will be added to powdered infant formula at a level not exceeding 16 g/100 g powder. The infant formula to be manufactured by ByHeart will have a hydration rate of 12.5 g powder/100 ml formula ready to consume; this level is equivalent to 2.0 g dry whole milk/100 ml formula ready to consume. When formulated with dry whole milk at the 16% usage rate, along with other nutrients, ByHeart's infant formula meets the regulatory requirements of human milk substitutes when fed as a sole source of nutrition from the first day of life in healthy term infants.*

22. ByHeart did not cite Fomon (1970), which showed that butterfat was an issue with fecal fat losses that could affect growth. Fomon, et al. found that when the formulation was modified and butterfat was kept to 50% or less and combined with vegetable oils, the fecal fat losses were reduced. While the notice focused on milk protein, it did not discuss issues with butterfat. Please provide a discussion regarding the fat from whole milk and how ByHeart's formulation level of this fat is safe.

Response:

The conditions for the potential for fat malabsorption noted in Fomon et al. (1970) do not apply for several reasons listed below. We believe that OFAS's interpretation is inconsistent with the conclusions by Fomon et al (1970). Formulations studied by Fomon et al. (1970) contained 100% fat from either the butterfat or from vegetable oils; none of the formulas included a mixture of butterfat and vegetable oils.

Fomon et al. (1970) noted that fat excretion would not be a concern "when adequate calories are provided from diets that offer no more than 40% of calories from butterfat and no more than 50% of calories from vegetable oils." ByHeart's whole milk powder provides only 12% of total fat in the final infant formula. With this usage rate in the infant formula, 51% of total calories will be from the two combined fat sources, in compliance with infant formula regulations. Thus, 6% of the total calories are provided by butterfat and the remaining 45% of total lipid calories are from vegetable oil.

Additionally, Fomon et al. (1970) recommended not feeding infants homogenized or evaporated milk without the addition of carbohydrate. The final ByHeart infant formula also contains lactose, a source of carbohydrate, and is not fed as a sole source of nutrition like the homogenized or evaporated milk studied by Fomon et al. (1970), thereby muting conditions of fecal fat excretion as noted in the study.

Test	AOAC Method - Eurofins	Method Noted by OFAS	Exact words from OFAS "Please confirm that the cited methodologies for specification parameters are the most recent and validated for the test article. For many of the specifications listed in the notice, multiple methods are cited, which have differing conditions or applicability."	Eurofins Comments:
Moisture determination	AOAC 925.09 (Moisture of Flour) and 926.08 (Moisture of Cheese)	AOAC 927.05 (Moisture in Dried Milk)	**Bullet 1** The methods listed for moisture determination are AOAC 925.09 (Moisture of Flour) and 926.08 (Moisture of Cheese). We note AOAC 927.05 (Moisture in Dried Milk) may be a more appropriate alternative.	These different AOAC moisture methods all use convection oven drying to a constant weight at 100 ºC. They will all produce equivalent results.
Protein determination	AOAC 968.06 (Protein (Crude) in Animal Feed) and 992.15 (Crude Protein in Meat and Meat Products Including Pet Foods)	AOAC 975.17 (Protein in Milk), AOAC 2016.15 (Quantification of Whey Protein Content in Milk-Based Infant Formula Powders).	**Bullet 2** The methods listed for protein determination are AOAC 968.06 (Protein (Crude) in Animal Feed) and 992.15 (Crude Protein in Meat and Meat Products Including Pet Foods). We note possible alternatives that may be more appropriate, including AOAC 975.17 (Protein in Milk), AOAC 2016.15 (Quantification of Whey Protein Content in Milk-Based Infant Formula Powders).	The Eurofins AOAC method utilized Dumas combustion technology which is the "industry standard" for the determination of protein. AOAC Method 975.17 uses a spectrophotometric method, which is very non-specific. This method is no longer widely used. AOAC 2016.15 is a method used to separate whey and casein, and not valid for the determination of total protein. Eurofins has extensive experience measuring protein in milk powder using combustion technology.
Ash determination	AOAC 923.03 (Ash of Flour).	AOAC 945.46 (Ash of Milk) or AOAC 930.30 (Ash of dried milk).	**Bullet 3** The method listed for ash determination is AOAC 923.03 (Ash of Flour). We note possible alternatives that may be more appropriate, including: AOAC 945.46 (Ash of Milk) or AOAC 930.30 (Ash of dried milk).	These different AOAC ash methods are all essentially identical. They all ash the samples at 550 ºC to a constant weight. The results from all of these methods will be virtually the same.

iron, sodium, and potassium determination	AOAC 984.27 (Calcium, Copper, Iron, Magnesium, Manganese, Phosphorus, Potassium, Sodium, and Zinc in Infant Formula), AOAC 985.01 (Metals and Other Elements in Plants and Pet Foods), and AOAC 2011.14 (Ca, Cu, Fe, Mg, Mn, K, P, Na, and Zn in Fortified Food Products).	We note method AOAC 985.01 does not include iron or sodium, and that a possible alternative that may be more appropriate would be AOAC 2015.06 (Minerals and Trace Elements in Milk, Milk Products, Infant Formula, and Adult/Pediatric Nutritional Formula).	**Bullet 4** The methods listed for determination of iron, sodium, and potassium include AOAC 984.27 (Calcium, Copper, Iron, Magnesium, Manganese, Phosphorus, Potassium, Sodium, and Zinc in Infant Formula), AOAC 985.01 (Metals and Other Elements in Plants and Pet Foods), and AOAC 2011.14 (Ca, Cu, Fe, Mg, Mn, K, P, Na, and Zn in Fortified Food Products). We note method AOAC 985.01 does not include iron or sodium, and that a possible alternative that may be more appropriate would be AOAC 2015.06 (Minerals and Trace Elements in Milk, Milk Products, Infant Formula, and Adult/Pediatric Nutritional Formula).	The principle of the Eurofins method is AOAC 984.27, which is designed to measure all of the elements in infant formula using ICP-AES. In addition to infant formula, this method has been used extensively on milk powder. Eurofins has extensive experience using AOAC Method 984.27 for the analysis of Fe, Na, and K in milk powder. The other methods listed by Eurofins are for reference only.
Chloride determination	AOAC 963.05 (Chlorides in Tobacco), AOAC 971.27 (Sodium Chloride in Canned Vegetables), and AOAC 986.26 (Chloride in Milk-Based Infant Formula).	We note a possible alternative that may be more appropriate to be AOAC 2016.03 (Chloride in Milk, Milk Powder, Whey Powder, Infant Formula, and Adult Nutritionals).	**Bullet 5** The methods listed for determination of chloride include AOAC 963.05 (Chlorides in Tobacco), AOAC 971.27 (Sodium Chloride in Canned Vegetables), and AOAC 986.26 (Chloride in Milk-Based Infant Formula). We note a possible alternative that may be more appropriate to be AOAC 2016.03 (Chloride in Milk, Milk Powder, Whey Powder, Infant Formula, and Adult Nutritionals).	The AOAC method that is used by Eurofins involves a potentiometric titration procedure. The other AOAC methods that are listed use an identical technology and will produce comparable results. Eurofins has extensive experience using this method to measure chloride in milk powder.

Heavy metals determination	AOAC 993.14 (Trace Elements in Waters and Wastewaters) and AOAC 2011.19 (Chromium, Selenium, and Molybdenum in Infant Formula and Adult Nutritional Products	The older method does not include mercury and the latter method is specifically for determination of chromium, selenium, and molybdenum. We note possible alternatives that may be more appropriate, including AOAC 2013.06 (Arsenic, Cadmium, Mercury, and Lead in Foods) and AOAC 2015.01 (Heavy metals in food), which includes infant formula but does not include mercury as an analyte.	**Bullet 6** The methods listed for determination of heavy metals include AOAC 993.14 (Trace Elements in Waters and Wastewaters) and AOAC 2011.19 (Chromium, Selenium, and Molybdenum in Infant Formula and Adult Nutritional Products). The older method does not include mercury and the latter method is specifically for determination of chromium, selenium, and molybdenum. We note possible alternatives that may be more appropriate, including AOAC 2013.06 (Arsenic, Cadmium, Mercury, and Lead in Foods) and AOAC 2015.01 (Heavy metals in food), which includes infant formula but does not include mercury as an analyte.	The AOAC method that Eurofins uses involves a microwave digestion followed by analysis of the heavy metals using an ICP-MS. All of the other AOAC methods listed all use the identical technologies and would produce comparable results. Eurofins has extensive experience using this method for the analysis of heavy metals in milk powder and has validated this procedure to include mercury.
iodide determination	AOAC 2012.15 (Total Iodine in Infant Formula and Adult/Pediatric Nutritional Formula).	Byheart ask is to confirm acceptable for Dried Whole Milk		Eurofins developed and validated AOAC Method 2012.12 for the analysis of iodine. It has been used extensively in measuring iodine in milk powder.

Respectively submitted,

(b) (6)

April 7, 2021

Darryl Sullivan

Chief Science Officer

Eurofins Scientific

(b) (6)

April, 7th, 2021

RE: OFAS Response

To Whom It May Concern,

(b) (4) meets or exceeds all Grade "A" Pasteurized Milk Ordinance (PMO) requirements. In addition, (b) (4) & our farms are certified organic & regulated under the National Organic Program (NOP). Lastly, (b) (4) & our farms have 3rd party Grass-fed certification which adds an additional level of requirements & oversight. (b) (4) confirms that:

- The raw milk utilized for making dry whole milk meets US regulatory limits for veterinary drug residues, pesticides and is tested per the requirements in the Grade "A" PMO.
- The raw milk utilized for making dry whole milk is produced in accordance with good agricultural practices and the requirements outlined under the National Organic Program section 7 CFR § 205.240.
- The raw milk utilized for making dry whole milk complies with the derived intervention level for radionuclides (CPG 555.880 which replaces CPG 560.750).
    - NOP section 7 CFR §205.105: does not allow for Ionizing radiation to be considered for organic certification.
    - Our farms are not located near any nuclear facilities or nuclear waste storage locations.
    - Any testing shall be completed by the customer.

(b) (4)

(b) (6)

(b) (6)

- To the best of our knowledge, raw milk utilized for making dry whole milk meets pesticide tolerances specified in 40 CFR Part 180 for milk.
    - The Grade "A" PMO and NOP section 7 CFR § 205.670 both require periodic pesticide testing at the producer level & farm level. (b) (4) (b) (4) and affiliate farms all abide and meet the requirements outlined in the regulations.
    - In addition, organic farmers are greatly limited in the type of pesticides allowed for use by the NOP. Section 7 § 205.601-205.604 describe the allowed and prohibited substances.
    - Any additional testing outside of Grade "A" PMO or NOP program shall be completed by the customer.

Please do not hesitate to contact me with further questions.

(b) (6)

(b) (6)

(b) (6)

From: jheimbach@va.metrocast.net
To: Morissette, Rachel; jh@jheimbach.com
Cc: "Jeanne Hoskin"; Gyan Rai; "Ron Belldegrun"
Subject: RE: [EXTERNAL] RE: call to discuss GRN 000980
Date: Tuesday, May 25, 2021 8:25:49 AM
Attachments: image001.png
Morissette Rachel 20210525.pdf
OFAS GRN980 Final Response.pdf
[redacted]Letter.pdf

Dear Rachel—

Here is ByHeart's response to FDA's questions discussed on May 14. There are three attachments:

- A cover letter addressed to you
- ByHeart's responses to the questions
- An unredacted copy of the certification from [redacted]

We are confident that we have provided satisfactory responses to FDA's concerns.

Regards,
Jim

James T. Heimbach, Ph.D., F.A.C.N.
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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, May 14, 2021 10:52 AM
To: jh@jheimbach.com
Subject: RE: [EXTERNAL] RE: call to discuss GRN 000980

Hi Jim,

Thanks again for the call this morning to discuss FDA's questions below. Hopefully we all have a better understanding of the intent behind the questions and how best to address them. As Jeanne mentioned, we'll expect to see ByHeart's response by May 26th. Have a great weekend.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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FDA U.S. FOOD & DRUG ADMINISTRATION

JHeimbach LLC

May 25, 2021

Rachel Morissette, Ph.D.
Division of Food Ingredients
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park MD 20740

Dear Dr. Morissette:

This letter is ByHeart's response to the questions posed by FDA reviewers during our last discussion regarding GRN 980.

In addition to the responses that follow, we have attached to our email a document that may not have been successfully pasted into our response, a Milk Supplier's Certificate from [redacted] that addresses the sourcing of our milk and its compliance with Pasteurized Milk Ordinance requirements. (This latter document is an unredacted version of the document previously supplied.)

We are confident that we have provided satisfactory responses to your questions. If anything is unclear, we will be happy to provide explanation.

Sincerely,

(b) (6)

James T. Heimbach, Ph.D., F.A.C.N.
President

cc. Jeanne Hoskin, Ph.D.
Gyan Rai, Ph.D.
ByHeart, Inc.

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1. In response to our question 15, ByHeart states the following:

   > "We confirm that the correct method for the determination of iodide is AOAC 2212.15, not the method cited in the notice (AOAC 2012.15); this was a typographical error. This method is also in updated Table 2 in the response to Q7."

   This response is still citing the incorrect method for iodide, though the error was fixed in the revised Table 2 in the response to question 7. Please correct this statement to reflect the correct method citation for iodide.

   ByHeart Response: Apologies for the oversight- the statement should read as follows:

   > "We confirm that the correct method for the determination of iodide is AOAC 2012.15, not the method cited in the notice (AOAC 2212.15); this was a typographical error. This method is also in updated Table 2 in the response to Q7."

2. In response to our question 17, ByHeart provides a Milk Supplier Certificate with supplier information redacted. While we agree that this information can remain confidential and the redacted version will be posted on our inventory, we request an unredacted version of this document for the administrative record.

   ByHeart Response: We are providing the unredacted version. We request that this information be used only for FDA's administrative records and remain confidential from the public notice and FOIA requests to the extent legally possible.

Milk Supplier OFAS Response FINAL.pdf

3. In Section 6.5.1 Evidence of Safety in the notice, ByHeart states:

> "In summary, the body of generally available evidence from history of use and controlled scientific studies support the safety of By Heart's intended use of dry whole milk."

However, as stated in our question 19, we have not identified any studies that used dry whole milk (not unmodified whole milk) under the proposed conditions of use (i.e., as a component of infant formula). As discussed in our pre-submission meeting on October 29, 2020, we indicated that if clinical studies are used to support safety, a thorough discussion of the test article and how it relates to the notified ingredient is needed. Additionally, we note that based on the response provided to question 19, it now appears that ByHeart is making the argument that the safety profile of its dry whole milk is the same as dry nonfat milk, which is already a component of infant formula. Finally, we note that certain modifications were deemed necessary to make cow milk "safe and palatable for human infants," including: 1) removal of animal fat and substituting vegetable oils; 2) adjusting protein content to avoid renal overload; and 3) adjusting minerals & vitamins (i.e., iron, calcium, phosphorus, etc.) (Fomon, 2001; IOM, 2004; Martin et al., 2016).

Given that the compositional differences among unmodified milk, dry whole milk, and dry nonfat milk may potentially impact safety (van Lieshout et al. 2020) and that information noted above regarding cow milk appears counter to ByHeart's GRAS conclusion, please provide the following:

3a. A narrative outlining the similarities and differences among unmodified milk, dry whole milk, and dry nonfat milk and why any differences are not a safety concern for the intended use.

ByHeart Response:

In this GRAS notice (GRN 980), ByHeart intends to add dry whole milk to its infant formula at a maximum use level of 16 g dry whole milk/100 g formula powder. At this level, it becomes part of a complex mixture of the infant formula and contributes a portion of formula protein (26%), formula fat (12%), and formula lactose (8%). Additional ingredients are needed to meet infant formula requirements, and these are typically whey (contributing 74% of formula protein), vegetable oils (88% of formula fat), and lactose (92% of formula carbohydrate). Vitamins and minerals are added, and any slight innate contribution from dry whole milk is considered formulation overage.

ByHeart believes that the substantial cited literature in the notice that describes feeding infants unmodified liquid whole milk is supportive of the safety of dry whole milk, and therefore contributes to the totality of evidence for the safe use of dry whole milk as a constituent of infant formula.

Regarding any heat-processing effect on cow-milk proteins, the additional heat processing of spray drying has no or limited impact on milk protein denaturation and does not impact protein digestibility or bioavailability (van Lieshout et al., 2020). The drying step only removes the moisture from the unmodified liquid whole milk with limited additional heat impact.

The effects of spray drying as well as other heat processes on milk proteins are summarized in the van Lieshout et al. (2020) review. These include pasteurization at variable times and temperatures, sterilization (intense heating process for extended times), dry dairy processing (i.e., spray drying), and storage of sterilized or dry milk powders. It is important to note that pasteurization and/or sterilization are common steps in the manufacture of unmodified and dry milks.

ByHeart's dry whole milk powder processing conditions are consistent with industry practice for the standard heat processing of milk and whey powders. Consistent with van Lieshout et al. (2020) and the Dairy Processing Handbook[1], minimal if any protein denaturation occurs under standard liquid processing of unmodified whole milk and subsequently during its spray-drying. Further, ByHeart's dry whole milk in not stored for prolonged periods, nor it is stored at high ambient temperatures. It is typically consumed in infant formula production within a few months of packaging and is stored at normal ambient temperatures (10-30^{o}C and relative humidity <70%). Thus, in terms of the heat treatment, the safety profiles of unmodified milk, nonfat dry milk, and dry whole milk are comparable.

The notifier summarizes in the table below the effects of heat processing conditions, as reviewed by van Lieshout et al. (2020; Tables 2 & 3 of the review paper), in unmodified whole milk, dry whole milk, and nonfat dry milk.

SIMILARITIES AND DIFFERENCES OF HEAT PROCESSING ON UNMODIFIED MILK, DRY WHOLE MILK, AND DRY NONFAT MILK

<table>
<tr><th>Processing Type</th><th>Unmodified whole milk</th><th>Dry whole milk and dry nonfat milk (no specific differences noted)</th></tr>
<tr><td>Liquid heat processing (pasteurization)</td><td colspan="2">Major milk proteins remain in native state. Because of lack of tertiary structure, caseins do not typically denature and aggregate on heating.

Whey proteins can form disulfide bridges on heating.

Whey proteins (beta lactoglobulin) may aggregate on casein micelle surfaces, as driven by disulfide bridge (S-S) formation.

Intense heating (long times, high temperatures) may lead to partial or full denaturation of whey proteins (unfolding). High heat processing can also oxidize all protein sources resulting in an almost complete modification of methionine, tyrosine, and tryptophan.</td></tr>
<tr><td>Evaporation</td><td>Not evaporated</td><td>Evaporation may cause protein denaturation to be partial.

Evaporation causes some disulfide bond (S-S) aggregation – whey proteins aggregate on casein micelles (otherwise caseins are not directly affected by pasteurization conditions)</td></tr>
</table>

[1] MILK AND WHEY POWDER | Dairy Processing Handbook (tetrapak.com)

Processing Type	**Unmodified whole milk**	**Dry whole milk and dry nonfat milk (no specific differences noted)**
Drying	Not dried	Glycation and oxidation may occur during drying. Rate of protein denaturation is lower than in liquid milk (most denaturation occurs during liquid heating step)
Storage	Not stored (fresh)	Protein denaturation is not affected by storage. Protein aggregation and chemical modifications may occur. Glycation leads to browning when milk powders are stored at high temperatures for long times.
Digestion differences/gastric hydrolysis and emptying	Digestion differences/gastric hydrolysis and emptying may be slower with less heat, but generally the effect of heating liquid milk on intestinal hydrolysis is small. (Non-heated whey proteins are still intact after gastric digestion.)	Digestion differences/gastric hydrolysis and emptying are increased with heating (mainly for whey proteins). Conflicting results on whether whey-casein aggregates formed during heating results in decreased hydrolysis of caseins.
Protein digestibility and biological value	Protein digestibility and biological value is the same; in animals different heated milks did not affect overall digestibility or protein digestibility except in intense heat processing of milk proteins. Oxidation of proteins, especially of casein, can affect overall digestibility.	
Overall physiological activity of milk proteins	Overall physiological activity of milk proteins needs intense heat processing for peptides to induce physiological responses along GI tract	
Allergenicity	Intensive and prolonged heating of milk proteins may affect the immune system and their allergenic potential through advanced glycation end products.	

Potential Physiological Consequences:

While there are slight differences introduced for spray-dried powders in protein aggregation or denaturation, the overall effect on the nutritional quality of the powder is largely similar in terms of protein digestibility and bioavailability. Van Lieshout et al. (2020) also mention that while glycation occurs differentially in heat-treated liquid v/s powder infant formula, protein digestibility of the powder is significantly higher in comparison with liquid infant formula. The authors also note that while Maillard conjugation could improve gastric digestibility of whey proteins, it is more likely related to the heat-induced denaturation of the whey proteins. In relation to casein digestion, whey-casein aggregates formed during heating are postulated to decrease hydrolysis; however, the authors also note that this conflicts with the results of other studies. Furthermore, the paper also notes that denaturation does not affect overall digestibility although it may affect digestion kinetics. These results have been observed despite different flocculation behaviors of the skimmed milk powders that were differently heat treated. The authors note that while heat does have an impact during milk processing, they did not identify any specific differences on milk protein that affects overall protein digestibility and bioavailability. The authors also note that while drying may enhance chemical modifications like glycation and oxidation, the rate of denaturation is lower than in liquid dairy products. For protein denaturation in dried dairy products, the heating intensity of the liquid process is a major factor, with limited or no further denaturation occurring during the drying process itself. Additionally, the authors note that for sterilized or dry dairy products, sensitivity of milk protein to denaturation is observed when they are stored for a prolonged period at high ambient temperatures.

In summary, the van Lieshout et al. (2020) analysis of 102 studies shows that heat processing affects milk proteins to varying degrees, and thus may impact protein digestibility and quality (bioavailability). However, the paper also suggests that while studying the modifications of specific cow milk proteins on the developing digestive and immune systems in infants is a worthwhile effort, there is no indication from these 102 studies that anything other than the extreme or high intensity of heat processing, and not the milk source (unmodified milk, dry whole milk, nonfat milk, WPC, or liquid and powder infant formula), has potential to impact milk proteins and their physiological consequences.

Finally, we note that in relation to certain modifications that were deemed necessary to make cow milk "safe and palatable for human infants," including: 1) removal of animal fat and substituting vegetable oils; 2) adjusting protein content to avoid renal overload; and 3) adjusting minerals & vitamins (i.e., iron, calcium, phosphorus, etc.), IOM (2004) is only referring to the early use of cows' milk as a poor substitute for sole source nutrition in infants and before the advent or availability of infant formulas. Indeed today, unmodified whole milk would continue to be a poor human milk substitute as a sole source of nutrition. By purposeful design, the addition of dry whole milk at 16 g dry whole milk/100 g formula powder concentration in infant formula powder provides only 26% of total formula protein, and supplementation of whey sources is required to meet the compositional requirements for total formula protein and the desired 80:20 whey:casein ratio. Furthermore, the dry whole milk addition to ByHeart's infant formula provides only 12% of total formula fat; the remainder is provided by vegetable oils, and together this combination meets the infant formula compositional requirements for total formula fat and fat calories. The potential renal solute load of the ByHeart infant formula was calculated at 20.3 mOsm/100 kcal, which is within the acceptable range of 20-26 mOsm/100 kcal as reported by Zeigler and Fomon (1989)[2] or IOM (2004). Finally, minerals such as iron,

[2] Ziegler EE, Fomon SJ., Potential renal solute load of infant formulas. (1989) J Nutr. 119(12 Suppl):1785-8

calcium, and phosphorus are added to meet the infant formula compositional requirements, including the Ca:P ratio between 1.1-2.0.

Finally, it should be noted that, in accordance with IOM (2004) guidelines and infant formula requirements, a Protein Efficiency Ratio (PER) per AOAC Method 960.48 was conducted on the ByHeart infant formula that contained dry whole milk at the intended use level in this notice and where it contributed 26% of total formula protein, and the result was a PER greater than the casein control, establishing the sufficient biological quality of the protein in infant formula.

3b. A narrative outlining how the addition of ByHeart's dry whole milk ingredient to existing cow milk-based infant formulas is not expected to impact safety.

ByHeart Response:

Dry whole milk is intended to be added to the ByHeart infant formula at a level not exceeding 16 g dry whole milk/100 g formula powder. At this addition level, and at a final protein composition in infant formula of 2 g/100 kcal, the dry whole milk contributes 26% of total formula protein (i.e., 0.52 g/100 kcal infant formula) and the sole source of formula casein for a resulting whey:casein ratio of 80:20. The remainder of the protein sources used in ByHeart's infant formula are either GRAS or approved nutrients for infant formula use and their usage levels are in accordance with their respective GRNs or are consistent with infant formula feeding requirements[3,4]. Human milk contains a predominance of whey proteins, while cow milk has more casein (20:80 whey:casein ratio). Formulas with a whey:casein ratio similar to human milk were introduced in 1962 and by 2000 whey-predominant formulas were the most widely used milk-based formulas (IOM, 2004). The use of dry whole milk and whey powders does not differ from the traditional use of nonfat dry milk and whey powders. The contribution of casein from the dry whole milk in ByHeart's infant formula is, however, less than the contribution of casein from nonfat dry milk in existing infant formulas that typically have a whey:casein ratio of 60:40. If a current manufacturer wishes to add the maximum content of dry whole milk as in this notice, the manufacturer will also have to add some nonfat dry milk or casein to retain the 60:40 ratio. If the existing infant formula composition requires the complete replacement of nonfat dry milk (i.e., and retain the 60:40 ratio), a new safety determination will be required. Our GRAS determination does not provide for any use of dry whole milk at a level greater than 16 g dry whole milk/100 g formula powder.

[3] Martin, C.R., Ling, P.R., and Blackburn, G.L. (2016). Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. Nutrients *8*.

[4] Koletzko et al, (2005) Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group; ESPGHAN Committee on Nutrition; 41:584–599.

[redacted]

April, 7th, 2021

RE: OFAS Response

To Whom It May Concern,

[redacted] meets or exceeds all Grade "A" Pasteurized Milk Ordinance (PMO) requirements. In addition, [redacted] & our farms are certified organic & regulated under the National Organic Program (NOP). Lastly, [redacted] our farms have 3rd party Grass-fed certification which adds an additional level of requirements & oversight. [redacted] confirms that:

- The raw milk utilized for making dry whole milk meets US regulatory limits for veterinary drug residues, pesticides and is tested per the requirements in the Grade "A" PMO.
- The raw milk utilized for making dry whole milk is produced in accordance with good agricultural practices and the requirements outlined under the National Organic Program section 7 CFR § 205.240.
- The raw milk utilized for making dry whole milk complies with the derived intervention level for radionuclides (CPG 555.880 which replaces CPG 560.750).
    - NOP section 7 CFR §205.105: does not allow for Ionizing radiation to be considered for organic certification.
    - Our farms are not located near any nuclear facilities or nuclear waste storage locations.
    - Any testing shall be completed by the customer.

[redacted]

[redacted]

- To the best of our knowledge, raw milk utilized for making dry whole milk meets pesticide tolerances specified in 40 CFR Part 180 for milk.
    - The Grade “A” PMO and NOP section 7 CFR § 205.670 both require periodic pesticide testing at the producer level & farm level. [redacted] and affiliate farms all abide and meet the [redacted] outlined in the regulations.
    - In addition, organic farmers are greatly limited in the type of pesticides allowed for use by the NOP. Section 7 § 205.601-205.604 describe the allowed and prohibited substances.
    - Any additional testing outside of Grade “A” PMO or NOP program shall be completed by the customer.

Please do not hesitate to contact me with further questions.

[redacted]

[redacted]