# 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
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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.

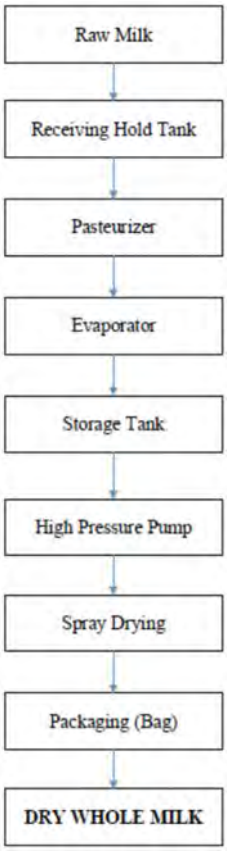



**Figure 1. Process Flow Diagram of ByHeart's Dry Whole Milk.**

### 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 90$^{th}$ 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:<br>1) Dried whole milk, potato flour, carrot flour, sucrose & veg oil<br>2) Wheat flour, pea flour, carrot flour, sucrose, & veg oil<br>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:<br>1) Whole milk & wheat noodles<br>2) Lactose-hydrolyzed whole milk & wheat noodles<br>3) Modified whole milk<br>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:<br>1) lowfat cow's milk<br>2) whole cow's milk<br>3) partially veg. fat milk<br>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 $\alpha_1$-antitrypsin (FA1AT) | 820 healthy infants aged 2 weeks to 12 months | Infants were receiving:<br>1) whole milk (n = 146)<br>2) breast milk (n = 354)<br>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

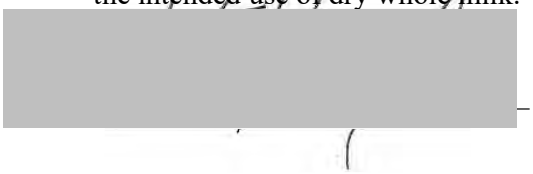
The intended addition of dry whole milk to nonexempt infant formula has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(b). This safety was shown by animal studies in rats and pigs; uncomplicated human digestion via well-established metabolic pathways without adverse 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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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: _____

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Ronald Kleinman, M.D.
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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 |