GRAS Conclusion for the Use of Dry Whole Milk as an Ingredient in Non-Exempt Infant Formula

PREPARED FOR:

Nara Organics, Inc.
335 Madison Avenue, 4th Floor
New York, NY 10017

SUBMITTED TO:

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
5001 Campus Drive
College Park, MD 20740

PREPARED BY AND CONTACT FOR TECHNICAL OR OTHER INFORMATION:

Mary M. Murphy, MS, RD
Exponent, Inc.
1150 Connecticut Avenue, NW
Washington, DC 20036

November 8, 2021

REDACTED VERSION

Table of Contents

List of Tables

List of Figures

List of Acronyms

ADPI	American Dairy Products Institute
AOAC	Association of Official Analytical Collaboration
bw	body weight
CFR	Code of Federal Regulations
CFU	colony forming unit
cGMP	current good manufacturing practices
CMMEF	Compendium of Methods for the Microbiological Examination of Foods
CLA	conjugated linoleic acid
DGA	Dietary Guidelines for Americans
DIAAS	digestible indispensable amino acid score
DWM	dry whole milk
EFSA	European Food Safety Authority
EVOH	ethylene-vinyl alcohol copolymer
FARE®	Foods Analysis and Residues Evaluation Program®
FDC	FoodData Central
FD&C	U.S. Federal Food, Drug, and Cosmetic Act
FDA	U.S. Food and Drug Administration
FITS	Feeding Infants and Toddlers Study
FOIA	Freedom of Information Act
g	gram
GMP	Good Manufacturing Practices
GRAS	Generally Recognized As Safe
GRN	GRAS Notice
HHS	U.S. Department of Health and Human Services
HM	human milk
HPLC	high-performance liquid chromatography
IF	infant formula
IOM	Institute of Medicine
ISO	International Organization for Standardization
kcal	kilocalorie
kg	kilogram
kJ	kilojoule
L	liter
LOQ	limit of quantification
LSRO	Life Sciences Research Office
m	meter
mcg	microgram

MFGM	milk fat globule membrane
mg	milligram
mL	milliliter
mOsm	milliosmole
MSNF	milk solids not fat
NCHS	National Center for Health Statistics
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NLT	not less than
NMR	nuclear magnetic resonance
NMT	not more than
NOP	National Organic Program
PDCAAS	protein digestibility amino acid score
PER	Protein Efficiency Ratio
pH	potential hydrogen
PMO	Pasteurized Milk Ordinance
ppm	parts per million
RTF	ready-to-feed
UL	tolerable upper intake level
umol	micromole
US	United States
USDA	United States Department of Agriculture
WMP	whole milk powder
WPC	whey protein concentrate
WWEIA	What We Eat in America

Part 1: Signed Statements and Certification

Nara Organics, Inc. submits to the U.S. Food and Drug Administration (FDA) this generally recognized as safe (GRAS) notice in accordance with 21 CFR part 170, subpart E.

Name and Address of Notifier

Nara Organics, Inc.
335 Madison Avenue, 4th Floor
New York, NY 10017

Notifier Contact:
Juan M Gonzalez, Ph.D.
Head of Research & Development
Nara Organics
335 Madison Avenue
4th Floor
New York, NY 10017
juan@naraorganics.com

with a copy to:
Jung Ma
Chief of Staff
Nara Organics
335 Madison Avenue
4th Floor
New York, NY 10017
jung@naraorganics.com

Agent Contact:
Mary M. Murphy, MS, RD
Exponent, Inc.
1150 Connecticut Avenue, NW
Washington, DC 20036
mmurphy@exponent.com

Name of GRAS Substance

The substance that is the subject of this GRAS notice is dry whole milk.

Intended Conditions of Use

The intended use of dry whole milk is as an ingredient in Nara Organics milk-based, non-exempt infant formula for healthy term infants at a maximum level of 22 g per 100 g infant formula powder.

Basis for Conclusion of GRAS Status

Nara Organics' conclusion of GRAS status for the intended use of dry whole milk in non-exempt infant formula for healthy term infants is based on scientific procedures in accordance with 21 CFR §170.30(a) and (b).

Pre-Market Approval Exclusion Claim

The intended use of dry whole milk in non-exempt infant formula is not subject to the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Nara Organics has concluded that such use is GRAS through scientific procedures.

Availability of Information

The data and information that serve as the basis for this GRAS conclusion will be sent to the FDA upon request, or are available for the FDA's review and copying during customary business hours at the office of Exponent, Inc., located at 1150 Connecticut Ave, NW, Washington, DC 20036.

Exemptions from Disclosure

Our view is that none of the data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the Freedom of Information Act (FOIA).

Certification Statement

On behalf of Nara Organics, I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, 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.

Name: Juan M. Gonzalez, Ph.D.

November 8th, 2021

Date:

Part 2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

Common or Usual Name

The substance that is the subject of this GRAS notice is dry whole milk.

Identity

Description

Dry whole milk is the product resulting from the removal of water only from pasteurized milk, which may have been homogenized, and is defined by the FDA under the standard of identity found at 21 CFR §131.147 to contain between 26% and 40% milk fat (by weight) on an "as is" basis and not more than 5.0% moisture (by weight) on a milk solids not fat (MSNF) basis. Dry whole milk contains lactose, milk proteins, milk fat, and milk minerals in the same relative proportions as the milk from which it was made. As specified in 21 CFR §131.147, dry whole milk may also 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 removal of water only from pasteurized milk, as defined in 21 CFR §131.110(a), which may have been homogenized. Additionally, as specified in 21 CFR §131.147, dry whole milk may contain added vitamin A, vitamin D and other optional ingredients.

U.S. standards for dry whole milk define "dry whole milk" (7 CFR §58.2701) as a substance that conforms to the provisions of 21 CFR §131.147 (USDA; Agricultural Marketing Service). Specifications for "U.S. Extra Grade" and "U.S. Standard Grade" also include limits for scorched particle count, solubility index, titratable acidity, flavor, appearance, bacterial estimates, and coliform count (7 CFR §58.2705) as presented in Table 1 below. As detailed in the table, select attributes of the dry whole milk including moisture, scorched particle content, solubility index, titratable acidity, appearance, and bacterial estimate, distinguish U.S. Standard Grade from U.S. Extra Grade.

Dry whole milk is sometimes referred to as whole milk powder, provided such product is not adjusted for protein[1]. Whole milk powder is defined by the CODEX Alimentarius Standard 207-1999, with the main difference that it contains a minimum protein content and may be subject to

[1] American Dairy Products Institute (ADPI) Whole Milk Powder standard, page 49, "WMP produced without protein adjustment is equivalent to dry whole milk (DWM) and may be used interchangeably".

protein adjustment. In contrast, the federal standard of identity for dry whole milk does not permit protein adjustment and, accordingly, does not have minimum protein standards. The dry whole milk that is the subject of this GRAS notice meets the requirements under 21 CFR §131.147 for dry whole milk. The dry whole milk contains protein, fat, lactose and minerals in the same relative proportions as the milk from which it is produced. It contains no added vitamin A, vitamin D, or other optional ingredients permitted in dry whole milk.

Table 1. U.S. standards for dry whole milk

Parameter	21 CFR §131.147	U.S. Standard Grade 7 CFR §58.2705	U.S. Extra Grade 7 CFR §58.2705
Moisture	≤5% by weight in milk solids-not-fat	≤5% by weight in milk solids-not-fat	≤4.5% by weight in milk solids-not-fat
Milk fat	≥26% to <40% by weight	≥26% to <40% by weight	≥26% to <40% by weight
Protein	No standardized protein level	No standardized protein level	No standardized protein level
Production	Produced from removal of water only from pasteurized milk (defined in §131.110(a), which may have been homogenized).	Produced from removal of water only from pasteurized milk (defined in §131.110(a), which may have been homogenized).	Produced from removal of water only from pasteurized milk (defined in §131.110(a), which may have been homogenized).
Scorched particle content	-	Max 22.5 mg for spray process	Max 15.0 mg for spray process
Solubility index (ml)	-	Max 1.5 mL for spray process	Max 1.0 mL for spray process
Titratable acidity	-	Max 0.17% (lactic acid)	Max 0.15% (lactic acid)
Optional Additions	Emulsifiers, stabilizers, anticaking agents, antioxidants, vitamin A, vitamin D, vitamin carriers, characterizing flavoring ingredients.	Emulsifiers, stabilizers, anticaking agents, antioxidants, vitamin A, vitamin D, vitamin carriers.	Emulsifiers, stabilizers, anticaking agents, antioxidants, vitamin A, vitamin D, vitamin carriers.
Modifications	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 removal of water only from pasteurized milk.	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 removal of water only from pasteurized milk.	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 removal of water only from pasteurized milk.

Parameter	21 CFR §131.147	U.S. Standard Grade 7 CFR §58.2705	U.S. Extra Grade 7 CFR §58.2705
Flavor	-	Reconstituted dry whole milk shall possess a sweet and pleasing flavor, but may possess the following flavors to a slight degree: bitter, oxidized, scorched, stale, and storage; and to a definite degree: cooked and feed.	Reconstituted dry whole milk shall possess a sweet, pleasing and desirable flavor, free from undesirable flavors, but may possess a slight feed flavor and a definite cooked flavor.
Physical appearance	-	Dry whole milk should be white or light cream color, but may possess a slight unnatural color; and shall be free from lumps that break up readily under moderate pressure; and reasonably free from visible dark particles. The reconstituted product shall be reasonably free from graininess.	Dry whole milk shall possess a uniform white to light cream color. It shall be free from lumps, except those that readily break up with slight pressure, and be practically free from visible dark particles. The reconstituted product shall be free from graininess.
Bacterial estimate	-	≤50,000 per gram standard plate count	≤10,000 per gram standard plate count
Coliform count	-	≤10 per gram	≤10 per gram

Source

Nara Organics dry whole milk is sourced from dairy cows and is processed in accordance with the Pasteurized Milk Ordinance (PMO) as a “Grade A” product. The PMO is the milk sanitation standard for Grade “A” milk and milk products used by the National Conference on Interstate Milk Shipments program. Further information regarding source of the dry whole milk is provided in the section titled “Specifications”, under “Monitoring of Potential Contaminants”.

Composition

Dry whole milk is a food and compositional data for this food are reported in the publicly available literature, including USDA’s FoodData Central, a recognized repository of reference food composition data.

Food composition data on dry whole milk from USDA and analytical data on the dry whole milk that is the subject of this GRAS notice are summarized below, including proximates (Table 2), fatty acids (Table 3), amino acids (Table 4), and key micronutrients (Table 5).

In addition, analytical data from three non-consecutive batches of the dry whole milk intended for use in infant formula are also presented in these tables, as represented by the average and range of the three samples. Since dry whole milk is derived from bovine biological secretions, there is inherent variability in the nutrient composition of this natural product. Reference nutrient composition values for dry whole milk from the USDA are presented as point estimates, which do not reflect such natural variability. Cow breed, environment and management, animal health and physiology, and nutrition are among the factors contributing to variability in the nutritional composition of dairy products (Linn, 1988). Thus, while the range of analytical values reported for the three dry whole milk samples includes the USDA reference value for some results summarized in Tables 2-5, some nutrient ranges vary from the reference point estimates as expected. The analytical data demonstrate that the dry whole milk samples are consistent with the 21 CFR §131.147 definition of dry whole milk based on the concentration of moisture (as set out in Table 2) and milk fat (as set out in Table 7), while the concentrations of other nutritional components are generally comparable to levels indicated by the USDA values.

Macronutrients

Table 2. Typical proximate composition of dry whole milk, g per 100 g

Component	Nara Organics Dry Whole Milk Sample Average[a]	Nara Organics Dry Whole Milk Sample Range[a]	Reference Values from USDA[b]
Moisture	2.7	2.4 - 2.8	2.47
Protein	26.2	25.6 - 27.1	26.3
Fat	30.1	29.7 - 30.3	26.7
Carbohydrate[c]	35.8	34.7 - 36.7	38.4
Ash	5.3	5.1 - 5.4	6.08

[a] Values reflect average and range of 3 samples from non-consecutive batches.
[b] Values as reported for Milk, dry, not reconstituted, whole; FDC ID: 1097874; FDC Published:10/30/2020 (USDA, 2021).
[c] Calculated for each sample as 100 – (moisture + protein + fat +ash).

Fatty Acids

Table 3. Typical fatty acid composition of dry whole milk, g per 100 g

Component[a]	Nara Organics Dry Whole Milk Sample Average[b]	Nara Organics Dry Whole Milk Sample Range[b]	Reference Values from USDA[c]
10:0 Capric	0.88	0.87 -0.89	0.60
12:0 Lauric	1.02	1.00 -1.03	0.61
14:0 Myristic	3.13	3.09 - 3.21	2.82
16:0 Palmitic	8.26	7.82 - 8.98	7.52
18:0 Stearic	2.79	2.52 - 3.07	2.85
16:1 Palmitoleic	0.36	0.33 - 0.41	1.20
18:1 Oleic	4.91	4.6 - 5.11	6.19
18:2 Linoleic	0.59	0.55 - 0.62	0.46
18:3 Alpha Linolenic	0.20	0.18 - 0.21	0.20
Saturated Fatty Acids (Acid Form)	17.9	17.4 - 18.3	16.7
Monounsaturated Fatty Acids (Acid Form)	5.63	5.37 - 5.77	7.92
Polyunsaturated Fatty Acids (Acid Form)	0.83	0.79 - 0.87	0.67
Trans Fatty Acids (Acid Form)	1.21	1.13 -1.32	-
Total Fatty Acids	26.9	26.5 -27.3	25.3

[a] Analysis of these components conducted using AOAC 996.06 (Hydrolytic Extraction Gas Chromatographic Method).
[b] Values reflect average and range of 3 samples from non-consecutive batches.
[c] Values as reported for Milk, dry, not reconstituted, whole; FDC ID: 1097874; FDC Published:10/30/2020 (USDA, 2021).

Amino Acids

Table 4. Typical amino acid composition of dry whole milk, g per 100 g

Component[a]	Nara Organics Dry Whole Milk Sample Average[b]	Nara Organics Dry Whole Milk Sample Range[b]	Reference Values from USDA[c]
Alanine	0.878	0.854 - 0.914	0.908
Arginine	0.959	0.938 - 0.981	0.953
Aspartic Acid	1.980	1.970 - 2.000	2
Cystine	0.206	0.181 - 0.240	0.243
Glutamic Acid	5.213	5.170 - 5.270	5.51
Glycine	0.500	0.488 - 0.515	0.557
Histidine	0.695	0.67 0- 0.728	0.714
Isoleucine	1.387	1.360 - 1.430	1.59
Leucine	2.537	2.490 - 2.620	2.58
Lysine	2.117	2.040 - 2.270	2.09
Methionine	0.720	0.693 - 0.755	0.66
Phenylalanine	1.253	1.240 - 1.270	1.27
Proline	2.530	2.450 - 2.650	2.55

Component[a]	Nara Organics Dry Whole Milk Sample Average[b]	Nara Organics Dry Whole Milk Sample Range[b]	Reference Values from USDA[c]
Serine	1.390	1.370 - 1.420	1.43
Threonine	1.117	1.100 - 1.140	1.19
Tryptophan	0.342	0.339 - 0.346	0.371
Tyrosine	1.330	1.310 - 1.370	1.27
Valine	1.630	1.590 - 1.700	1.76

[a] Analysis of these components conducted by Eurofins using their method of analysis for amino acids and tryptophan, including through hydrolysis and HPLC.
[b] Values reflect average and range of 3 samples from non-consecutive batches.
[c] Values as reported for Milk, dry, whole, without added vitamin D; FDC ID: 173454, NDB Number:1212 (USDA, 2018). [Note: Amino acid values are not reported for Milk, dry, not reconstituted, whole; FDC ID: 1097874; FDC Published:10/30/2020. Macronutrient data reported in 2018 and 2020 do not differ, therefore the amino acid data are assumed to be representative of current dry whole milk].

Micronutrients

Table 5. Typical select micronutrient composition of dry whole milk, per 100 g

Component	Unit	Nara Organics Dry Whole Milk Sample Average[a]	Nara Organics Dry Whole Milk Sample Range[a]	Reference Values from USDA[b]
Vitamin A	IU	659	609 - 707	934
Vitamin D3	IU	<4.00	<4.00	20 [c]
Iron	mg	<0.248	<0.243 - <0.248 [d]	0.47
Iodine	mcg	186	155 - 244	-
Selenium	mcg	16.5	15.7 - 17.3	16.3
Sodium	mg	274	265 - 279	371
Potassium	mg	1133	1110 - 1160	1330
Chloride	mg	729	705 - 750	-

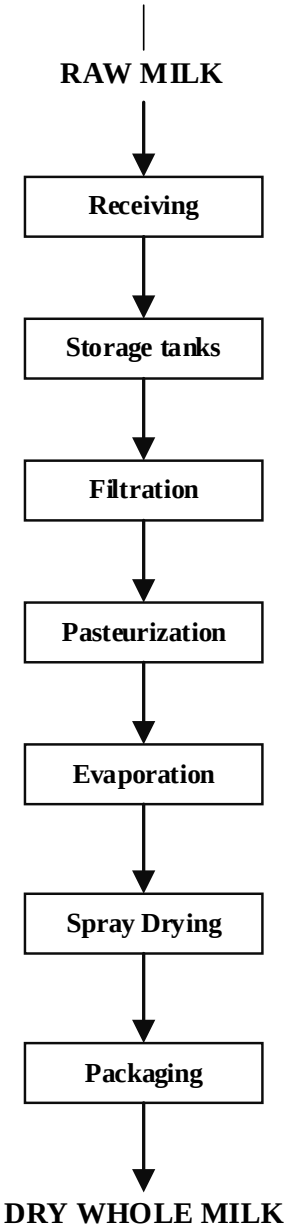
[a] Values reflect average and range of 3 samples from non-consecutive batches.
[b] Values as reported for Milk, dry, not reconstituted, whole; FDC ID: 1097874; FDC Published:10/30/2020 (USDA, 2021).
[c] Value assumed to represent concentration in vitamin D-fortified milk.
[d] The limit of quantification (LOQ) for iron was reported as <0.243 (1 sample) and <0.248 (2 samples); the difference in the LOQ is due to small differences in the sample weights used in the analyses.

Production Process

The dry whole milk used by Nara Organics is manufactured under conditions of current Good Manufacturing Practices (cGMP) using standard processing techniques in the dairy industry at a facility which is audited by a third party certification body for food safety and quality.

Briefly, the starting material is raw milk. This raw milk is produced in accordance with good agricultural practices, filtered to remove suspended solid particles, and pasteurized (≥15 seconds at ≥161 °F) before undergoing an evaporation step to partially remove moisture. After evaporation, the pasteurized milk is then spray dried to further remove moisture and create a powder. During this process, no other material is added and no component is concentrated to greater than naturally occurring levels on a dry basis. The powder is packed under nitrogen to remove oxygen from the bag and support stability of the product. The production process is summarized in Figure 1.

Figure 1. Flow diagram of the production process of dry whole milk



Specifications

Product Specifications

Product specifications for dry whole milk that is the subject of this GRAS notice define the key parameters which characterize and substantiate the identity of the product. The physico-chemical and microbiological criteria and their limits have been established to ensure consistent safety and quality of the ingredient for the intended use in infant formula.

The Nara Organics dry whole milk specifications (Table 6) include parameters for moisture, milk fat, protein, scorched particles, titratable acidity, insolubility, ash, peroxide value, and select nutrients. Product specifications also include limits on heavy metals and potential microbiological contaminants.

All methods of analysis are validated for the intended use. The methods of analysis for moisture, milk fat, scorched particles, titratable acidity, and insolubility have been validated for analysis of milk powders and the method of analysis for protein is validated for use in milk. The methods of analysis for *Cronobacter* species and *Salmonella* are recommended methods for infant formula powder (CAC/RCP 66-2008). The Enterobacteriaceae method is specific to dairy products, while the other microbiological methods are general methods and are appropriate for food. The methods used to analyze ash, peroxide value, the specified nutrients, and heavy metals are established methods of analysis, and consistent with the methods used for the analysis of dry whole milk for use in infant formula (GRN 980).

Table 6. Specifications for Nara Organics dry whole milk intended for use in infant formula

Parameter	Specification	Method
Moisture	NMT 4.5%	AOAC 927.05
Milk fat	NLT 26 NMT 35%	AOAC 932.06
Protein	NLT 22% NMT 30%	AOAC 991.20
Scorched particles	NMT Disk B (15 mg)	ADPI
Titratable Acidity	NMT 0.15%	ISO 6092:1980
Insolubility Index	NMT 1.0 mL	ADPI
Ash	NMT 7%	AOAC 923.03
Peroxide Value	NMT 5 meq/kg fat	AOAC 965.33
Cholesterol	NMT 150 mg/100 g	AOAC 994.10
Vitamin A	NMT 1500 IU/100 g	AOAC 992.04, 992.06, 2001.13
Vitamin D3	NMT 10 IU/100 g	AOAC 2011.11
Iron	NMT 1 mg/100 g	AOAC 984.27, 985.01, 2011.14

Parameter	Specification	Method
Iodine	NMT 500 mcg/100 g	AOAC 2012.15
Selenium	NMT 30 mcg/100 g	AOAC 2011.19
Sodium	NMT 500 mg/100 g	AOAC 984.27, 985.01, 2011.14
Potassium	NMT 1600 mg/100 g	AOAC 984.27, 985.01, 2011.14
Chloride	NMT 1200 mg/100 g	AOAC 963.05, 971.27, 986.26
Microbiological		
Aerobic Plate Count	<10,000 cfu/g	ISO 4833:2003
Coliforms	<10 cfu/g	ISO 4832:2006
Yeast	<100 cfu/g	FDA BAM, Ch 18
Mold	<100 cfu/g	FDA BAM, Ch 18
Salmonella spp.	Negative / 375g	ISO (AFNOR) 160140/6579
Listeria monocytogenes	Negative / 25g	ISO (AFNOR) 160140/11290-1
Staphylococcus (Coagulase +)	<10 cfu/g	ISO 6888-1
Bacillus cereus	<100 cfu/g	ISO 7932
Enterobacteriaceae	<10 cfu/g	ISO 21528-2
Cronobacter spp	Not detected / 10g	ISO 22964:2017-04
Heavy Metals		
Lead	NMT 50 mcg/kg	AOAC 2011.19, 993.14
Arsenic	NMT 100 mcg/kg	AOAC 2011.19, 993.14
Cadmium	NMT 50 mcg/kg	AOAC 2011.19, 993.14
Mercury	NMT 50 mcg/kg	AOAC 2011.19, 993.14

Abbreviations: ADPI - American Dairy Products Institute; AOAC - Association of Official Analytical Collaboration; CMMEF - Compendium of Methods for the Microbiological Examination of Foods; ISO - International Organization for Standardization; NLT - not less than; NMT - not more than.

Analytical data from three non-consecutive lots as shown in Table 7 demonstrate the products comply with the stated specifications, indicating a production process that is in control and allows for consistent manufacturing of dry whole milk.

Table 7. Analytical results of three non-consecutive lots compared to Nara Organics dry whole milk specifications

Parameter	Nara Organics Specification	Analyzed Lots		
		2127210601	2127210711	2127192531
Moisture	NMT 4.5%	2.8	2.4	2.8
Milk fat	26 – 35%	30.2	29.7	30.3
Protein	22 – 30%	25.6	25.8	27.1
Scorched Particles	NMT Disk B (15 mg)	7.5	7.5	7.5
Titratable Acidity	NMT 0.15%	10	11	10
Insolubility Index	NMT 1.0 mL	0.1	0.1	0.175
Ash	NMT 7%	5.3	5.4	5.1

Peroxide Value	NMT 5 meq/kg fat	1.4	1.3	1.4
Cholesterol	NMT 150 mg/100 g	101	108	107
Vitamin A	NMT 1500 IU/100 g	662	707	609
Vitamin D3	NMT 10 IU/100 g	<4.00	<4.00	<4.00
Iron	NMT 1 mg/100 g	<0.248	<0.248	<0.243
Iodine	NMT 500 mcg/100 g	244	160	155
Selenium	NMT 30 mcg/100 g	15.7	16.4	17.3
Sodium	NMT 500 mg/100 g	265	279	278
Potassium	NMT 1600 mg/100 g	1130	1110	1160
Chloride	NMT 1200 mg/100 g	705	731	750
Microbiological				
Aerobic Plate Count	<10,000 cfu/g	210	150	130
Coliforms	<10 cfu/g	<10	<10	<10
Yeast	<100 cfu/g	<10	10	<10
Mold	<100 cfu/g	20	<10	<10
Salmonella spp.	Negative / 375g	Negative	Negative	Negative
Listeria monocytogenes	Negative / 25g	Negative	Negative	Negative
Staphylococcus (Coagulase +)	<10 cfu/g	<10	<10	<10
Bacillus cereus	<100 cfu/g	<100	<100	<100
Enterobacteriaceae	<10 cfu/g	<10	<10	<10
Cronobacter spp	Not detected / 10g	Not detected	Not detected	Not Detected
Heavy Metals				
Lead	NMT 50 mcg/kg	<5.00	<5.00	<5.00
Arsenic	NMT 100 mcg/kg	<10.0	<10.0	<10.0
Cadmium	NMT 50 mcg/kg	<5.00	<5.00	<5.00
Mercury	NMT 50 mcg/kg	<5.00	<5.00	<5.00

Abbreviations: ADPI - American Dairy Products Institute; AOAC - Association of Official Analytical Collaboration; ISO - International Organization for Standardization; NMT - not more than.

Monitoring of Potential Contaminants

Nara Organics routinely monitors dry whole milk for additional potential environmental contaminants to ensure hygienic control. For example, monitoring of aflatoxin M1 in dry whole milk samples demonstrates levels below the limit of detection of 0.05 mcg/kg, and monitoring of pesticide residues demonstrates levels below the limit of detection for the particular residue (such limit of detection being, typically, 0.005 mg/kg).

Additionally, the dry whole milk intended for use in infant formula is monitored under the pasteurized milk ordinance (PMO; 21 CFR §1240.61). The supplier of the milk for the dry whole milk product has confirmed that the milk is produced under provisions of the PMO, which includes the screening for veterinary drug residues and pesticides. The supplier of the milk also

complies with the National Organic Program (NOP) which does not allow for ionizing radiation in organic products (7 CFR §205.105). A redacted copy of the supplier letter confirming adherence to the PMO (Grade "A"), and NOP certification is provided in Appendix A.

Stability

The dry whole milk that is the subject of this notice is packaged in paper kraft bags which contain a food grade inner gas barrier consisting of a polyethylene outer layer and inner layers of nylon and ethylene-vinyl alcohol copolymer (EVOH) that provide an effective barrier against moisture, light, and contamination. The powder is further protected by nitrogen-flushing the bags to reduce the level of residual oxygen and protect against oxidation. Reduction of oxygen in the headspace of the dry whole milk bag reduces significantly the rate at which the powder may develop oxidized and other off-flavor notes (Lloyd *et al*., 2009). The dry whole milk that is the subject of this notice has a shelf-life of up to 2 years when stored in a cool, dry, odor-free environment. This shelf-life is consistent with other commercially available dry whole milk powders.

Part 3. Dietary Exposure

Proposed Use and Level

The dry whole milk that is the subject of this GRAS notice is intended for use as an ingredient in milk-based non-exempt infant formula for healthy term infants as a source of the macronutrients protein, fat, and carbohydrate. The maximum intended use of the dry whole milk in infant formula is 22 g per 100 g infant formula powder. The infant formula to be manufactured by Nara Organics will have a reconstitution rate of 13 g powder/100 mL formula ready to consume; the resulting use of dry whole milk will not exceed 2.9 g dry whole milk/100 mL infant formula ready to consume, or 4.3 g dry whole milk/100 kilocalories (kcal) infant formula given an energy density of 67.6 kcal/100 mL.

At this addition level, the mean protein contributed by the dry whole milk will be 49% of total protein and the sole source of casein protein in the milk-based infant formula. Other sources of whey proteins will be added to the infant formula to target a resulting whey:casein ratio of 60:40. The dry whole milk will also contribute a portion of the total fat (21%), and carbohydrate (16%) content of the infant formula. Other ingredients will be added (vegetable oils and lecithin to reach the desired fat content, and lactose to reach the desired carbohydrate content, and vitamins and minerals) to ensure the infant formula is nutritionally complete for infants and compliant with 21 CFR §107.100.

Estimated Daily Intakes

Dietary Recall Data

Intake of infant formula can be estimated using data collected in dietary recalls. The What We Eat in America (WWEIA) dietary recall component of the National Health and Nutrition Examination Survey (NHANES) provides nationally representative nutrition and health data that are used to develop prevalence estimates for nutrition and health status measures for the U.S. population, including infants ages 0-11 months in the first year of life.

Estimates of dry whole milk intake from the intended use in infant formula were developed from food consumption records collected in the WWEIA/NHANES conducted in combined cycles from 2011-2012 to 2017-2018, referred to as NHANES 2011-2018 (CDC, 2021). NHANES is a continuous survey though the data are released in cycles, with each cycle spanning two years of data collection. Use of four survey cycles (i.e., 8 years) provided for a larger sample of infants.

As part of the examination, trained dietary interviewers collected detailed information on all foods and beverages consumed by respondents in the previous 24-hour time period (midnight to midnight). A second dietary recall was administered by telephone three to ten days after the first dietary interview, but not on the same day of the week as the first interview. For participants under six years of age (including infants), interviews were conducted with a proxy. In the survey period 2011-2018, two complete days of dietary recalls as determined by the National Center for Health Statistics (NCHS) were provided for a total of 28,845 individuals, including a total of 1,194 infants 0-11 months of age at the time of the exam. The total sample of infants includes infants for whom only consumption of human milk was reported, as well as infants consuming foods (including infant formula) other than human milk or a combination of foods and human milk.

The survey data files processed by USDA provide the estimated energy intake for each item reported consumed in the dietary recall. All infant formulas (e.g., milk-based, soy-based, partially hydrolyzed) providing 65-67 kcal per 100 g food code, which is typical of the energy density of non-exempt infant formula in NHANES, were assumed to be interchangeable for the purposes of estimating energy intake to meet the needs of infants. This list of food codes (provided in Appendix B) was thus used to develop representative estimates of energy intake from infant formula. Infant formulas reported consumed in NHANES with higher levels of energy per 100 mL (as consumed) provided >70 kcal per 100 mL and were not representative of infant formula for healthy term infants, while infant formulas with a lower concentration of energy (<65 kcal per 100 mL) were typically formulas targeted for the transition from the infant to toddler stages. For each infant with a complete 2-day dietary recall, a 2-day average energy intake from the selected infant formula food codes (Appendix B) was derived by summing the reported energy intake from infant formula over the two 24-hour recalls and dividing the sum by two. The intake of dry whole milk from the intended use in infant formula was calculated assuming 67.6 kcal per 100 mL of formula and 2.9 g dry whole milk per 100 mL reconstituted infant formula.

Per "user" mean and 90th percentile 2-day average intakes were calculated for four subpopulations of infants: 0-2 months, 3-5 months, 6-8 months, and 9-11 months. Estimates were calculated as intake per day (kcal from infant formula/day, g dry whole milk as an ingredient in infant formula/day) and intake per kg bw per day (kcal from infant formula/kg bw/day, g dry whole milk as an ingredient in infant formula/kg bw/day). Per user estimates represent consumption among infants reported to consume infant formula on either of the survey days, and includes infants consuming infant formula as a sole source of nutrition or a component of nutrition (e.g., in combination with human milk and/or table foods). The estimates of infant formula intake were derived using the Foods Analysis and Residues Evaluation Program (FARE® version 14.06) software which uses statistically weighted values. The statistical weights

compensate for variable probabilities of selection, adjusted for non-response, and provide intake estimates representative of the U.S. population.

Estimated intakes of energy from infant formula based on NHANES 2011-2018 are summarized in Table 8 below. Among infants in the first three months of life (0-2 months), 54.3% of infants were reported to consume a representative infant formula at least once on the 2 days of dietary recall, while 60.7% of infants in the second three months of life (3-5 months) consumed a representative infant formula. In the second six months of life (6-8 months and 9-11 months), approximately 71-72% of infants were reported to consume a representative infant formula at least once during the dietary recalls. Infants not consuming infant formula presumably consumed human milk and/or table foods, or an infant formula excluded from this assessment.

The estimated energy intake from infant formula was highest among infants 3-5 months of age with mean and 90th percentile 2-day average intakes of 539 and 833 kcal/day, respectively. On a body weight basis, the highest energy intake from infant formula was among infants 0-2 months of age with mean and 90th percentile 2-day average intakes of 95 and 146 kcal/kg bw/day, respectively. Relative to intakes in the first six months of life, intake of infant formula in the second six months of life was lower expressed as both kcal per day and kcal per kg bw per day.

Table 8. Per user estimated daily intake of energy from infant formula, WWEIA/NHANES 2011-2018

		Users		Body weight, kg	kcal/day		kcal /kg bw/day	
Age, mo	Total Sample	Number	Percent		Mean	90th Percentile	Mean	90th Percentile
0-2	250	148	54.3	5.1	484	766	95	146
3-5	346	229	60.7	7.0	539	833	78	118
6-8	295	212	71.7	8.3	479	735	58	95
9-11	303	210	70.7	9.5	435	694	47	75

Abbreviations: WWEIA/NHANES - What We Eat In America / National Health and Nutrition Examination Survey.
Total sample represents number of infants with 2 days of recall data in the sample; Users number represents unweighted number of infants reporting use of infant formula on at least one day of dietary recall. Infants not consuming infant formula presumably consumed human milk and/or table foods, or an infant formula excluded from this assessment.

Per user intakes of dry whole milk from the intended use in infant formula were calculated from the estimated intakes of energy from infant formula and are summarized in Table 9. Per user mean intake of dry whole milk from the intended use in infant formula ranges from 19 to 23 g/day and the 90th percentile intake ranges from 30 to 36 g/day across the first year of life. Infants 3-5 months of age have the highest estimated intakes with mean and 90th percentile 2-day average dry whole milk intakes of 23 and 36 g/day, respectively. On a body weight basis, the highest estimated intake of dry whole milk from infant formula was among infants 0-2 months of

age with mean and 90th percentile 2-day average intakes of 4.1 and 6.3 g/kg bw/day, respectively.

Table 9. Per user estimated daily intake of dry whole milk from the intended use in infant formula, WWEIA/NHANES 2011-2018

Age, mo	Users	g/day		g/kg bw/day	
		Mean	90th Percentile	Mean	90th Percentile
0-2	168	21	33	4.1	6.3
3-5	261	23	36	3.4	5.1
6-8	235	21	32	2.5	4.1
9-11	234	19	30	2.0	3.2

Abbreviations: WWEIA/NHANES - What We Eat In America / National Health and Nutrition Examination Survey.
Assumptions: 2.9 g dry whole milk/100 mL infant formula as consumed, and 67.6 kcal per 100 mL.

Summary of Estimated Daily Intakes

Estimates of energy intake from select infant formulas representative of typical non-exempt infant formula as captured in WWEIA/NHANES 2011-2018 for subpopulations of infants ages 0-2 months, 3-5 months, 6-8 months, and 9-11 months were used to estimate intake of dry whole milk from the intended use in infant formula, namely 2.9 g dry whole milk per 100 mL infant formula and assuming 67.6 kcal per 100 mL. These estimates show that approximately 54-61% of infants consume a representative infant formula in the first six months of life and approximately 71-72% of infants consume a representative formula in the second six months of life. These estimates are generally consistent with data from the nation-wide cross-sectional Feeding Infants and Toddlers Study (FITS) showing use of infant formula by 62.2% and 64.7% of infants in the first and second six months of life, respectively, in a sample of 1502 infants (Anater *et al*., 2018; Kay *et al*., 2018).

Using WWEIA/NHANES 2011-2018 data, the estimated mean intake of energy from infant formula among consumers of infant formula was 484-539 kcal/day among infants in the first six months of life, and 435-479 kcal/day in the second six months of life. The estimated mean energy intake from infant formula based on FITS is likewise generally consistent at 528 and 531 kcal/day, respectively (Kay *et al*., 2018), demonstrating that intakes of energy from infant formula developed with the WWEIA/NHANES 2011-2018 data are consistent with data in the published literature. Given the increasing energy requirements throughout the first 12 months of life (IOM, 2005), the data also indicate that infant formula accounts for a decreasing proportion of total energy needs in the second six months of life as reported in the literature (Grimes *et al*., 2015; Kay *et al*., 2018).

Based on energy intakes from formula and the proposed use of dry whole milk, the maximum mean and 90th percentile 2-day average intake of dry whole milk by infants is among the subpopulation of infants 3-5 months of age with intakes of 23 and 36 g/day, respectively. The maximum mean and 90th percentile 2-day average intake of dry whole milk on a bodyweight basis is among infants 0-2 months of age at 4.1 and 6.3 g/kg bw/day, respectively.

The intended use of dry whole milk is as an ingredient at up to a level of 22 g per 100 g infant formula powder. As such, it will be one of many ingredients in a complex mixture developed to meet the infant's nutritional needs. Based on the typical concentration of macronutrients in dry whole milk, the maximum intended use of dry whole milk in the infant formula, and the total nutrient profile of the infant formula, the dry whole milk ingredient will contribute a portion of the formula's total protein (49%), fat (21%), and carbohydrate (16%).

Nutrients in Dry Whole Milk and Maximum Allowable Levels in Infant Formula

As specified in 21 CFR §107.100, milk-based infant formulas are required to provide select micronutrients including vitamin A, vitamin D, iron, iodine, selenium, sodium, potassium, and chloride below maximum specified levels per 100 kcal infant formula (Table 10). The average concentration of these nutrients in dry whole milk and the estimated concentration per 100 kcal infant formula provided by the intended use of dry whole milk, as well as the maximum concentration of each nutrient in dry whole milk and the corresponding concentration per 100 kcal infant formula, are summarized in Table 10.

The regulations in 21 CFR §107.100 specify maximum allowable levels for protein and fat at 4.5 g per 100 kcal and 6.0 g per 100 kcal (54% of kcal as fat), respectively. As reported in Table 6, the maximum concentration of protein per 100 g of dry whole milk is 30 g, and the maximum concentration of fat per 100 g of dry whole milk is 35 g. At the maximum intended use of dry whole milk in infant formula, dry whole milk will account for no more than 1.3 g of protein per 100 kcal of formula and no more than 1.5 g of fat per 100 kcal (14% of kcal). These data demonstrate that at the maximum intended use of dry whole milk, the naturally occurring levels of macronutrients and micronutrients observed in the dry whole milk will contribute some of the required nutrients in infant formula while not exceeding the maximum permitted levels for any micronutrients with a regulatory maximum.

Table 10. Nutrients in dry whole milk and potential concentration in infant formula vs maximum permitted concentration

Component	Unit	Average Nutrient Concentration in Nara Organics Dry Whole Milk		Maximum Nutrient Concentration in Nara Organics Dry Whole Milk		Maximum permitted level per 100 kcal (21 CFR §107)
		per 100 g dry whole milk[a]	per 100 kcal infant formula[b]	per 100 g dry whole milk[c]	per 100 kcal infant formula[b]	
Vitamin A	IU	659	28	1500	64	750
Vitamin D3	IU	4	0.17	10	0.43	100
Iron	mg	0.248[d]	0.01	1	0.04	3.0
Iodine	mcg	186	8	500	21	75
Selenium	mcg	16.5	0.7	30	1	7
Sodium	mg	274	12	500	21	60
Potassium	mg	1133	49	1600	69	200
Chloride	mg	729	31	1200	51	150

[a] Values reflect average of 3 samples from non-consecutive batches; see Table 5.
[b] Shown as dry whole milk contribution to Nara Organics infant formula. Calculated values in infant formula assume 4.3 g dry whole milk per 100 kcal infant formula.
[c] Values reflect maximum concentration per product specifications; see Table 6.
[d] Represents maximum limit of quantification for values reported as below the limit of quantification (< LOQ).

Part 4. Self-Limiting Levels of Use

The amount of dry whole milk which may be added to a milk-based infant formula is limited by the nutrient requirements as set out in 21 CFR §107.100 and the desired whey to casein protein ratio of the infant formula. Targeting a mid-lactation mature human milk whey to casein protein ratio of 60:40, the limit of dry whole milk use in a milk-based infant formula would be constrained by both the maximum protein content set out under 21 CFR §107.100 and the whey to casein protein ratio typically found in bovine milk (i.e., 20:80). The dry whole milk that is the subject of this notice is for use in infant formula up to 22 g per 100 g infant formula powder.

Part 5. Experience Based on Common Use in Food before 1958

The conclusion of GRAS status for the use of dry whole milk as an ingredient in non-exempt infant formula is based upon scientific procedures. Examples of common use in food before 1958 are provided in Part 6 as supplemental information.

Part 6. Narrative

Historical Use of Milk in Infant Formula

Human milk is recognized as the gold standard for infant feeding though the feeding of human milk is not always feasible or desired. Infant formulas are designed to duplicate as much as possible the nutrient profile of human milk. The nutritive and non-nutritive profile of human milk is complex, and in turn, a complex formulation of ingredients is required to replicate the natural substance.

Milk and milk products have a long history of use in the U.S. food supply, including consumption by infants and toddlers in the transition from a diet of exclusive human milk and formula to foods. Throughout this dossier, reference to "milk" other than human milk refers to cow's milk, which is referenced in some literature as bovine milk.

Infant formula feeding practices in the U.S. have not recently relied on the use of whole milk or milk fat, though historically substitutes for human milk have included cow's milk which could also be in the forms of evaporated milk and sweetened milk (Innis, 2011; IOM, 2004; Jensen and Jensen, 1992). In the early 1900s, cow's milk was recognized as the most likely foundation for development of infant formula (IOM, 2004). The modern commercial milk-based infant formulas originated with the development of a formulation called "synthetic milk adapted" which contained nonfat cow's milk, lactose, and fat from vegetable oils. Further modifications to the cow's milk base continued over time, including but not necessarily limited to modifications such as changes in the fatty acid profile, dilution of protein and altering the whey:casein ratio to mimic the ratio in human milk, and adjusting levels of micronutrients. Cow's milk-based formulas produced from nonfat milk and milk-derived ingredients remain the primary source of nutrition for formula fed infants (Corkins and Shurley, 2016; LSRO, 1998; Martin *et al*., 2016). Data collected in 2003-2010 indicate that cow's milk formula was used by 69% of infants fed formula or milk (Rossen *et al*., 2016). Dry skim milk is typically the predominant ingredient in milk-based formulas, though these formulas typically contain several other milk-derived ingredients such as whey and lactose, which are the predominant sources of protein and carbohydrate, respectively, in milk-based infant formula.

The intended use of dry whole milk, at a maximum use level of 22 g per 100 g infant formula powder as an ingredient in Nara Organics milk-based, non-exempt infant formula is suitable as the sole source of nutrition from the first day of life for healthy term infants. Nonfat skim milk is used as an ingredient in infant formula principally as a source of high quality protein and some carbohydrate. Similarly, the use of dry whole milk as an ingredient in infant formula will also provide high quality protein, some carbohydrate, and some lipid. Unfortified dry milk (whole or

skim) is also a source of naturally occurring vitamins and minerals, though the concentrations are low and fortification of the infant formula is necessary to achieve regulatory compositional requirements and meet infant nutrition needs.

Although commercial infant formulas moved away from the use of whole milk and related products in the 1970s, nonfat milk has been routinely used in infant formula as a source of protein and carbohydrate in the form of lactose for decades (Corkins and Shurley, 2016; LSRO, 1998).

Regulated Uses of Milk and Milk-Derived Ingredients in Infant Formula

Regulatory Status in the United States

As reviewed above, milk-based infant formulas are the predominant type of infant formula used in the U.S. These products are typically produced from a variety of milk-derived ingredients, including nonfat milk, various forms of whey, and lactose, which are GRAS affirmed substances for use in conventional foods. More recently, several ingredients derived from milk, including dry whole milk, have been recognized as GRAS for use in infant formula.

The use of dry whole milk as an ingredient in cow milk-based, non-exempt infant formula for term infants at a maximum level of 16 g per 100 g of powdered infant formula was concluded to be GRAS in 2020 (ByHeart, 2020). FDA was notified of the conclusion, which was filed as GRN 980. FDA reviewed the notice and responded with a "no questions" letter. The intended use of dry whole milk as detailed in GRN 980 is equivalent to 3 g dry whole milk per 100 kcal infant formula as consumed, with the dry whole milk providing 26% of the total formula protein, 12% of the total formula fat, and 8% of the total formula lactose.

The use of anhydrous milk fat as a source of fat in cow milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants at a maximum level of 7.0% by weight of the fat blend in formulas containing up to 50% of kcal as fat was concluded to be GRAS in 2019 (Hogan Lovell, 2019). FDA was notified of the conclusion, which was filed as GRN 898. FDA reviewed the notice and responded with a "no questions" letter. The intended use of anhydrous milk fat as detailed in GRN 898 provides an estimated 0.47 g anhydrous milk fat/kg bw/day, or up to 4.2 g anhydrous milk fat/day for an infant weighing up to 9 kg.

These GRNs and details on the GRAS status of other milk-derived ingredients for use in infant formula are summarized in Table 11 below.

Table 11. GRAS Notices (GRNs) for use of milk and milk-derived ingredients in infant formula

GRN No.	Substance	Intended Use	Date of Closure
980	Dry whole milk	Intended for use as an ingredient in cow milk-based, non-exempt infant formula for term infants at a maximum level of 16% (w/w) of powdered infant formula.	7/13/2021
898	Anhydrous milk fat	Intended for use as a source of fat in cow milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants at a maximum level of 7% of the fat blend	10/28/2020
669	Cows milk-derived lactoferrin	Ingredient in cows milk-based non-exempt infant formula for term infants at a level of 100 mg/100 g formula solids, which corresponds to approximately 13-14 mg/100 mL infant formula (ready-to-feed (RTF) or prepared for consumption from powder or liquid concentrate), and in follow-on formula at a level of 15 mg/100 mL RTF or prepared for consumption from powder.	3/9/2017
465	Cow's milk-derived lactoferrin	As an ingredient in cow's milk-based term infant formulas at a level of 100 milligrams (mg) per 100 grams (g) powdered formula, 26 mg per 100 milliliters (ml) liquid concentrate, and 13 mg /100ml ready-to-feed formula	2/18/2014
281	*Lactobacillus rhamnosus* strain HN001 produced in a milk-based medium	Ingredient in milk-based powdered term infant formula that is intended for consumption from the time of birth, as well as in milk-based powdered follow-on formula, at a level of 10^8 colony forming units per gram of the formula powder	8/31/2009

Dry Whole Milk in Infant Formula Outside of the U.S.

Several infant formulas made with dry whole milk are available outside of the U.S., including products marketed by Kendamil (United Kingdom), A2 Infant Formula (Australia), and Bellamy's Organic Infant Formula (Australia), either domestically or in export markets.

Assessment of Safety of the Intended Use of Dry Whole Milk

The use of dry whole milk, made from Grade "A" milk and meeting specifications as defined in GRN 980, was concluded to be safe for the intended use as an ingredient at a level of 16 g per 100 g infant formula powder by ByHeart. Multiple lines of evidence support the safety of the intended use of dry whole milk in GRN 980, including evidence that infants, children, and adults have consumed whole milk and dry whole milk without adverse effect other than allergic reactions in some susceptible individuals. Published clinical studies of infants consuming whole milk or components of whole milk were cited in support of the safety of whole milk as a component of the diet. ByHeart also reviewed potential concerns raised with the use of whole milk as a sole source of nutrition (e.g., potential nutrient deficiency, potential renal solute load,

fat absorption) and presented data showing that the intended use of dry whole milk as an ingredient in a complex infant formula provides only a portion of nutrients in the total formula. In addition, ByHeart reviewed the contributions of milk fat and lipid components of whole milk in infant formula. Physico-chemical similarities and differences between unmodified milk, dry whole milk, and nonfat dry milk arising from processing were discussed as were potential physiological consequences; any effects on processing were concluded to have no effect on the safety profile of the various forms of milk. ByHeart also noted that the use of dry whole milk is not different from the current use of nonfat dry milk and whey powders in infant formula, thus suggesting that the use of dry whole milk would be substitutional for other milk-based powders currently used in infant formula. We concur with the conclusion of safety as summarized in GRN 980 and the supplemental communications with FDA.

The evidence to support the safety of the intended use of dry whole milk as an ingredient in the infant formula for this GRAS notice is reviewed below. A series of literature searches was conducted in PubMed to identify more recent information pertinent to the safety review; a summary of the PubMed search strings used to identify literature for this review is provided in Appendix C. Additional searches, including searches of the FDA and general searches of the Internet, also were conducted. The more recent literature identified in these searches is incorporated in the discussion below.

Digestion of Milk in Infant Formula

The intended use of dry whole milk in infant formula would replace nonfat milk commonly used in milk-based formulations. Like nonfat milk, dry whole milk will provide milk protein and lactose in infant formula. Dry whole milk will also contribute fat to the total fat profile of the infant formula.

Protein

Consistent with the intended use detailed in GRN 980, the intended use of dry whole milk in this GRAS notice is use as an ingredient in infant formula and, as an ingredient, the dry whole milk will contribute to the overall nutrient profile of the infant formula. Nara Organics dry whole milk is manufactured using standard processes in the dairy industry that have been extensively reviewed for their effect on milk proteins and are consistent with the processes detailed in GRN 980 for the production of dry whole milk. Processing may affect milk proteins, and in turn these effects on milk proteins may have physiological effects. These effects of processing, including similarities and differences between dry whole milk, dry nonfat milk and whole milk (unmodified) are discussed below based on the review by van Lieshout *et al*. (2020).

Heat Processing Effects

Milk proteins are subjected to a variety of heat processes as part of standard dairy practices. All liquid dairy, like that used in the Nara Organics dry whole milk, undergoes a pasteurization step. During this processing step the naturally occurring casein (80% of the protein) and whey (20% of the protein) are subjected to a heating process. Because of a lack of tertiary structure, the caseins are remarkably stable; however, whey proteins are highly sensitive to pasteurization temperatures and tend to easily denature onto the casein micelles. It is important to note that all dairy products subjected to liquid pasteurization undergo the same changes, thus dry nonfat milk and dry whole milk subjected to similar processing conditions would be expected to have comparable changes in their protein profiles.

In contrast to liquid dairy products, powdered dairy products including dry whole milk and dry nonfat milk undergo the additional steps of evaporation and drying. Following drying, some powdered dairy products may be stored. As summarized by van Lieshout *et al*. (2020), the liquid pasteurization step causes the most protein denaturation. Evaporation can lead to partial protein denaturation and can cause some intermolecular disulfide bond formation. More specifically, whey proteins deposit onto casein micelles. The drying process leads to minimal or no further denaturation; however, during drying, chemical modifications such as glycation (known as the Maillard reaction) and oxidation may occur. Both modifications can cause a decrease in protein digestibility and amino acid availability and thus a decrease in protein quality but the proteins in both dry nonfat milk and dry whole milk undergo these same chemical modifications. Storage does not affect protein denaturation; however, depending on temperature and powder moisture content, there may be protein aggregation and chemical modifications, with glycation being the most common.

Potential Physiological Consequences

Milk proteins in general are recognized as highly digestible and high quality proteins for human nutrition. Typical processing may modify dairy proteins and in turn protein digestibility or kinetics (van Lieshout *et al*., 2020). The digestible indispensable amino acid score (DIAAS) and protein digestibility amino acid score (PDCAAS) are measures that have been used to evaluate the relative nutritional quality of different protein sources. PDCAAS and DIAAS data indicate that skim milk powder, whole milk powder, and fluid milk have comparably high scores (Burd et al., 2019; FAO/WHO 2013).

Research specifically on milk proteins in infant or enteral formula indicates that heating leads to protein denaturation that may enhance digestibility although heat-induced protein-protein and protein-lipid interactions may counteract this effect (Rudloff and Lonnerdal, 1992; Wada and Lonnerdal, 2014). Glycation of lysine and amino terminal residues, resulting from the heat-induced Maillard reaction, reduces the allergenicity of ß-lactoglobulin, the major milk allergen, by hindering the binding of IgE to the protein epitope; however, this glycation also reduces protein bioavailability (Sarwar et al, 1989; Perusko et al., 2018). This protein

bioavailability reduction is accentuated in liquid formula concentrates that are exposed to a higher heat process in comparison to a powdered formula (Sarwar *et al*., 1989, van Lieshout *et al*., 2019).

Summary

Overall, as discussed by van Lieshout *et al*. (2020) in a review of 102 peer-reviewed articles, processing affects milk proteins to varying degrees, which may in turn impact protein digestibility and quality and other physiological consequences of the proteins. Conditions of extreme or high intensity processing of milk protein may have the largest impact on physiological consequences. The more recent literature is consistent with these observations (e.g., Li *et al*., 2021). As noted above, the dry whole milk used by Nara Organics is processed and stored under practices routinely used in the processing of nonfat dry milk and whey powders commonly used as ingredients in infant formula. Any differences between dry whole milk and dry nonfat milk or unmodified milk are not expected to impact the ingredients with regard to their safety profile.

Additionally, consistent with quality factor requirements for infant formula (21 CFR §106.960), a Protein Efficiency Ratio (PER) bioassay was completed on the Nara Organics formula containing dry whole milk at the intended level of use. This study demonstrated that the PER was greater than that of the casein control, thus demonstrating appropriate biological quality of the protein required for an infant formula.

Milk is among the foods identified as a major allergen in the U.S. Allergy to milk protein is estimated to occur in approximately 2.6% of the population of young children in North America, though an estimated 5-15% of infants may experience cow's milk protein intolerance (Abrams and Sicherer, 2021; Corkins and Shurley, 2016). Infants exhibiting allergic reactions to cow's milk-based formula may be fed extensively hydrolyzed formulas or formulas containing non-milk sources of protein.

Fat

Recent studies describe the digestion of powder milk-based infant formulas with added milk fat compared to standard milk-based formula with vegetable fat and human milk. Using a static two-phase *in vitro* digestion model to mimic digestion in the gastric and duodenal phases of digestion, Hageman and colleagues (2019a; 2019b) showed that human milk and infant formula containing different fat blends result in a similar release of total fatty acids at the end of digestion as a percentage of initial composition. In this study, both infant formulas were powder-based and presumably skim milk-based (i.e., nonfat milk powder). One of the formulas contained only vegetable fat (palm, palm kernel, rapeseed, and sunflower oil) while the other formula contained a blend of 67% bovine milk fat and 33% vegetable fat (rapeseed, sunflower, and coconut oil). In comparisons of the percentage release of individual fatty acids from the two formulas,

differences in the release of some short and medium chain fatty acids were noted in the gastric and duodenal phases. However, following total digestion, the only difference between formulas was a lower percentage of C14:0 released from the formula containing milk fat compared to the formula containing only vegetable fat.

Liu and colleagues (2021) also examined *in vitro* digestion of human milk and infant formulas. Two infant formulas were prepared with whole bovine milk and whole goat milk, and two were prepared with skim milk. One of the skim milk-based formulas only had vegetable oils, while the other was formulated with milk fat globule membrane (MFGM) and vegetable oils. The lipolysis rate of human milk was highest at 86.8%, followed by the formula containing MFGM (81.2%), then the formulas containing whole milk (78.0% for the whole goat milk formula and 77.6% for the whole bovine milk formula), and lastly the skim milk, vegetable oil based formula (70.5%). The presence of MFGM components on the fat surface assisted with lipid hydrolysis. At the end of the simulated intestinal digestion, the concentration of palmitic acid was lower for human milk (158 umol/g) relative to all of the infant formulas, though the concentration from the formula containing a blend of whole bovine milk and vegetable fat and the formula containing only vegetable fat were comparable at 235 and 251 µmol/g, respectively.

Carbohydrate

Like nonfat milk, dry whole milk as an ingredient in infant formula will provide carbohydrate in the form of lactose. Lactose is the primary form of carbohydrate in human milk (Kien, 1996), and lactose is the common form of carbohydrate used in standard non-exempt infant formula (Corkins and Shurley, 2016). Lactose is recognized as safe and appropriate for use in infant formula for most healthy term infants (LSRO, 1998).

Unmodified Whole Milk vs Milk as an Ingredient

While infant feeding practices in the first half of the twentieth century commonly relied on use of evaporated milk or fresh cow's milk, evidence emerged that unmodified whole milk was not suitable as the sole source of nutrition for infants (Fomon, 2001; Ziegler, 2011). The intended use of dry whole milk in this GRAS notice is as one ingredient in infant formula, not as a sole source of nutrition. Nonetheless, concerns raised in the literature about the use of unmodified whole milk by infants are reviewed below to address any potential concerns regarding the intended use of dry whole milk as an ingredient.

Nutrient Imbalances including Iron Deficiency

Consumption of fresh milk by infants is associated with iron deficiency, potentially due to the low concentration of iron in milk, as well as iron inhibitors including calcium and casein and

intestinal blood loss (Ziegler, 2011). Clinical studies demonstrate that consumption of fresh milk results in early iron deficiency compared to consumption of a milk-based formula despite comparable intake of iron (Woodruff *et al*., 1972). Consumption of unmodified whole milk also was observed to result in a dose-dependent increase in intestinal blood loss among some infants, which could contribute to iron deficiency (Fomon, 1981; Wilson *et al*., 1974; Ziegler *et al*., 1990). In contrast to unmodified cow's milk, the study by Fomon and colleagues (1981) demonstrated that milk treated under time and temperature conditions consistent with those used in the manufacture of standard infant formula was not observed to cause fecal blood loss, thus suggesting that a heat-labile protein was at least in part a factor for the whole milk-induced bleeding. Other investigators also have observed a similar effect with heat-treated milk (Wilson *et al*., 1974). Studies on fecal iron loss show that the youngest infants exhibit the greatest loss, with concerns resolved by age 12 months (Jiang *et al*., 2000; Ziegler *et al*., 1999).

Regarding concerns of low iron, milk-based formulas fortified with iron at a concentration of 6 to 12 mg/L were observed to meet infants' iron needs (Ziegler, 2011). All non-exempt infant formulas are required to contain 0.15 to 3.0 mg iron per 100 kcal (21 CFR §107.100). If formula contains less than 1 mg of iron per 100 kcal, a statement on the label is required, "Additional Iron May Be Necessary", in order to ensure appropriate attention to infant iron needs. Non-exempt infant formulas are also required to contain certain micronutrients to ensure infant health. The low levels of other nutrients in milk that are important for infant health (e.g., vitamin C, zinc, vitamin E, essential fatty acids) are therefore not a concern. The Nara Organics infant formula will meet all nutrient specifications for infant formula listed in 21 CFR §107.100.

Potential Renal Solute Load

Additional concerns for infants consuming unmodified cow's milk include the high potential renal solute load which may contribute to the risk of dehydration. This risk has been considered a concern principally during illness (LSRO, 1998). The potential renal solute load of conventional infant formula (20-26 mOsm/100 kcal) was concluded to be an acceptable range (IOM, 2004; Ziegler and Fomon, 1989). The potential renal solute load of Nara Organics infant formula was estimated to be 21.4 mOsm/100 kcal which is within the acceptable range.

Avoiding Animal Fat

An additional concern regarding the use of whole milk as "safe and palatable for human infants" was identified as a need to remove animal fat and substitute butterfat (i.e., milk fat) with vegetable oils. Several reasons were cited to support the use of vegetable oils in infant formulas rather than milk fat; namely vegetable fats provided higher concentrations of unsaturated fatty acids, avoided a potential source of dioxins, resolved concerns around the odor of regurgitated

butterfat and perceptions of constipation resulting from feeding evaporated milk, and helped control cost (Hageman *et al*., 2019c).

Metabolic studies in infants also provide evidence that consumption of exclusively undiluted whole milk could not be promoted due to fecal fat loss. As summarized by Fomon and colleagues (Fomon *et al*., 1970), studies in infants demonstrate that consuming homogenized milk with 100% of fat as butterfat (milk fat) results in elevated fecal fat excretion. Relative to undiluted whole milk, intake of evaporated milk resulted in less fecal fat loss and formulations containing milk as an ingredient, *i.e.*, liquid or dry milk with added carbohydrate, did not result in fecal fat loss consistent with malabsorption. In a later review of infant nutrition, Fomon (1993) noted that the newborn infant's absorption of 100% milk fat is poor. However, when provided in formula as a blend of 50% milk fat and 50% vegetable oil (equal parts corn and coconut oil), the fat blend was well absorbed and excretion of fat was within the range of excretion from human milk and infant formula. Assuming that the fat blend accounted for approximately 50% of total energy in the formula, milk fat provided approximately 25% of total energy in the formula concluded to be well absorbed. The intended use of dry whole milk in infant formula will provide an estimated 10% of total energy from milk fat given that 49% of total energy in the formula is provided by fat and 21% of fat in the formula is provided by dry whole milk. The amount of milk fat provided by the intended use of dry whole milk is within the level of milk fat identified as well absorbed and therefore does not present a safety concern.

Components in Dry Whole Milk Not Found Presently in Typical Formula

In cow's milk, the lipid fraction is present predominantly in the form of globules secreted from the epithelial cells of the mammary gland (Le Huërou-Luron *et al*., 2018). The core of these milk fat globules contains fatty acids principally (~96-98%) in the form of triglycerides and smaller concentrations of other constituents including mono- and diglycerides and free fatty acids. The lipid globules are surrounded by the MFGM, a double layer of phospholipid membrane embedded with glyco-proteins, glyco-lipids, and cholesterol. The lipid globules also contain other constituents including carotenoids mainly as beta-carotene, sterols mainly as cholesterol, fat soluble vitamins including vitamins A, E, D, and K, and flavor compounds (Mohan *et al*., 2020). Overall, the core accounts for 94-98% of the globule mass, with the MFGM that surrounds it accounting for the balance. The MFGM consists primarily of phospholipids, in particular glycerolphospholipids and sphingolipids; about 60-70% of the phospholipids in milk are in the MFGM (Contarini and Povolo, 2013; Mohan *et al*., 2020).

Infant formulas manufactured with milk-derived ingredients such as skimmed milk and vegetable oils are estimated to contain up to 4% residual milk fat (Berger *et al*., 2000) and thus provide infants some exposure to components naturally present in dairy fat that are not found in

vegetable oils. Components unique to milk fat include short- and medium-chain fatty acids, branched- and odd-chain fatty acids, *trans* fatty acids, conjugated linolenic acid (CLA), as well as phospholipids, cholesterol and sphingolipids, which are largely found in the MFGM (Jensen *et al*., 1991; Gallier *et al*., 2020).

While the specific composition of cow's milk differs from the composition of human milk, these constituents in cow's milk fat are present at some concentration in human milk; thus breastfeeding infants are routinely exposed to these constituents. A review of the concentration of each constituent in non-exempt infant formula from the intended use of dry whole milk relative to the concentration in human milk provides information on the relative exposure to these substances and is discussed below.

Fatty Acids and Cholesterol

Milk fat is a source of several fatty acids that are not common to vegetable oils typically used in the manufacture of infant formula, namely butyric acid, *trans*-fatty acids, conjugated linoleic acid, odd-chain fatty acids, and branched-chain fatty acids (Gallier *et al*., 2020). The concentration of select fatty acids including butyric acid, *trans* fatty acids, CLA, odd chain fatty acids and cholesterol in dry whole milk intended for use in infant formula was examined and results are summarized in Table 12.

Table 12. Concentration of fatty acids and cholesterol in dry whole milk

Component[a]	Unit	Analyzed Lots[b]			
		2127210601	2127210711	2127192531	Average
4:0 Butyric	mg/100 g	1280	1160	1120	1187
Trans fatty acids (acid form)	mg/100 g	1320	1180	1130	1210
18:2 Conjugated Linoleic Acid	mg/100 g	204	197	151	184
15:0 Pentadecanoic	mg/100 g	325	342	368	345
17:0 Heptadecanoic	mg/100 g	165	163	186	171
Cholesterol	mg/100 g	101	108	107	105

[a] Fatty acids analyzed using AOAC 996.06 (Hydrolytic Extraction Gas Chromatographic Method), and cholesterol using AOAC 994.10.
[b] Values for 3 non-consecutive batches.

Based on the maximum intended use of dry whole milk in infant formula, the concentrations of these fatty acids and cholesterol provided from dry whole milk in infant formula were estimated and the percent of total fatty acids in the Nara Organics infant formula was calculated (Table 13). For comparison, the concentrations of these components in human milk and infant formula were summarized from the literature (as a percent of total fatty acids). The data demonstrate that these components of cow's milk fat also are present in human milk, and in varying concentrations in

infant formulas prepared from a variety of fat sources. With the exception of butyric acid, the intended use of dry whole milk will result in concentrations of these components well within or below the range of mean concentrations typically reported in human milk. The intended use of dry whole milk will result in a concentration of butyric acid in infant formula similar to the upper end of the mean concentration reported in human milk, and in the range of concentrations reported in infant formula containing milk fat (bovine or goat sources). Therefore, the intended use of dry whole milk in infant formula will provide these fat components at concentrations within the range of concentrations at which infants have been exposed.

Table 13. Estimated concentrations of select fatty acids and cholesterol in infant formula based on the intended use of dry whole milk with comparison to concentrations in human milk

Component	mg per 100 g dry whole milk[a]	Calculated mg per 100 mL Nara Organics infant formula[b]	Calculated % of fatty acids in Nara Organics infant formula[c]	Range of means in human milk (% of fatty acids)[d]	Range of means in infant formula (% of fatty acids)[e]
4:0 Butyric	1187	34.4	0.93	0.0009 - 0.76	ND - 3.1
Trans Fatty Acids (Acid Form)	1210	35.1	0.95	1.9 - 2.7	ND - 1.56
18:2 Conjugated Linoleic Acid	184	5.3	0.14	0.07 - 0.49	ND - 0.33
15:0 Pentadecanoic	345	10.0	0.27	0.08 - 0.50	ND - 0.6
17:0 Heptadecanoic	171	5.0	0.13	0.19 - 0.41	ND - 0.4
Cholesterol	105	3.0	-	9 - 20 mg per 100 mL	1.46 - 5.1 mg per 100 mL

[a] Mean of analytical values from 3 non-consecutive batches (see Table 12).
[b] Shown as dry whole milk contribution to Nara Organics infant formula. Calculated values in infant formula assume 2.9 g dry whole milk per 100 mL.
[c] Shown as dry whole milk contribution to Nara Organics infant formula fatty acid profile. Calculated values in infant formula assume 28 g fatty acids per 100 g infant formula.
[d] Concentrations in human milk (Chardigny *et al*., 1995; Glew *et al*. 2011; Hageman *et al*., 2019c; IOM, 2005; Koletzko, 2016; Martysiak-Zurowska *et al*., 2018; Mosley *et al*., 2005; Mueller *et al*. 2010; Prentice *et al*., 2019; Ratnayake *et al*., 2014; Santillo *et al*., 2018; Sun *et al*., 2016; Wan *et al*., 2010; Yuhas *et al*., 2006 [adapted from GRN 898]).
[e] ND = not detected; Claumarchirant et al., 2015; Gallier *et al.*, 2020; Hageman *et al.*, 2019c; Rodríguez-Alcalá et al., 2019; Martysiak-Zurowska *et al*., 2018; McGuire et al., 1997; Sun *et al*., 2016.

Phospholipids

Whole milk is a source of phospholipids including phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylinositol, phosphatidylserine, and sphingomyelin. The concentration of phospholipids in dry whole milk intended for use in infant formula was examined and summarized in Table 14 below. The predominant phospholipids are phosphatidyl-choline,

phosphatidylethanolamine, and sphingomyelin, which is consistent with the concentration of phospholipids in dry whole milk as reported by Soga and colleagues (2015).

Table 14. Concentration of phospholipids in dry whole milk

Component	Unit	Analyzed Lots[a]				Reference values per 100 g dry whole milk[b]
		2127210601	2127210711	212719531	Average	
Phosphatidylcholine	mg/100g	68	70	70	69	67
Phosphatidylethanolamine	mg/100g	65	54	50	56	63
Phosphatidylinositol	mg/100g	14	17	20	17	37
Phosphatidylserine	mg/100g	25	26	20	24	33
Sphingomyelin	mg/100g	53	62	60	58	57
Sum of Phospholipids	mg/100g	230	240	230	233	286

[a] Values for 3 non-consecutive batches. Phospholipid content was analyzed by NMR spectrometry.
[b] Values as reported by Soga *et al*., 2015.

Based on the maximum intended use of dry whole milk in infant formula and compositional data on the dry whole milk (Table 14), the concentration of phospholipids from dry whole milk in infant formula was estimated (Table 15). For comparison, the concentration of phospholipids as reported in human milk also is presented in the table. These data indicate that the concentration of phospholipids in infant formula is lower than the typical concentration provided in human milk.

Table 15. Estimated concentrations of phospholipids in infant formula based on the intended use of dry whole milk with comparison to concentrations in human milk

Component	mg per 100 g dry whole milk	Calculated mg per 100 mL infant formula[a]	Reference values mg per 100 mL human milk[b]
Phosphatidylcholine	69	2.0	3.3
Phosphatidylethanolamine	56	1.6	7.0
Phosphatidylinositol	17	0.5	0.8
Phosphatidylserine	24	0.7	3.8
Sphingomyelin	58	1.7	6.2
Sum of Phospholipids	233	6.8	21.6

[a] Shown as dry whole milk contribution to Nara Organics infant formula. Calculated values in infant formula assume 2.9 g dry whole milk per 100 mL.
[b] Average concentration of phospholipids reported by Ma *et al*., 2017 in human milk samples collected from transitional milk and mature milk at 2, 6, and 12 months of lactation.

Consumption of Whole Milk by Infants

Clinical studies in which infants and young children consumed bovine whole milk were identified and summarized in GRN 980. The more recent literature also was reviewed though no more recent interventions were identified. Among the 23 studies cited in GRN 980, eight studies represented prospective interventions in infants, including seven repeat intake studies with intake from 6 days to one year and one study examining acute effects of milk consumption. Key details from the eight prospective randomized trials, including infants (<12 months of age) in the study population, are presented in Appendix D.

Findings from these studies demonstrate that whole milk consumed as part of the diet by infants with gastrointestinal concerns including acute diarrhea or gastroenteritis (Alarcon *et al*., 1991; Brown *et al*., 1991; Hjelt *et al*., 1989; Isoulauri *et al*., 1986) did not result in adverse effects. Consumption of fortified whole milk was also observed to be well tolerated and result in less iron deficiency anemia when provided in a 12-month intervention (Stekel *et al*., 1988), and supported growth when provided for 3 months to infants with a mean age of 9.1 months (Larnkjær *et al*., 2009). As previously reviewed, Fomon and colleagues (1981) and Ziegler and colleagues (1990) provided evidence to establish that consumption of fluid pasteurized milk may contribute to iron deficiency in infants and is therefore not recommended. In contrast to unmodified cow's milk, the study by Fomon and colleagues (1981) demonstrated that fecal blood loss was mitigated in milk treated under time and temperature conditions consistent with those used in the manufacture of standard infant formula.

In addition to the prospective randomized trials including infants fed whole milk, GRN 980 summarized one non-English language paper describing a prospective randomized trial of 190 infants fed whole milk supplemented with iron and vitamin C (Hertrampf *et al*., 1990), and four observational studies including infants given whole milk (Bonuck *et al*., 2014; Maulen-Radovan *et al*., 1999; Penrod *et al*., 1990; Thomas *et al*., 1986). No adverse events attributable to the feeding of whole milk were noted in these studies.

GRN 980 also summarized nine studies in which toddlers or young children were given whole milk (Houghton *et al*., 2011; Svahn *et al*., 2000; Torres *et al*., 1995; van der Gaag and Forbes 2014; van der Gaag *et al*., 2017; van der Gaag *et al*., 2020; Vanderhout *et al*. 2016a; Vanderhout *et al*. 2016b; Wong *et al*., 2019) and no adverse effects attributable to whole milk were noted. In a more recent publication, Vanderhout and colleagues (Vanderhout *et al*., 2020) note that a higher intake of cow-milk fat is associated with lower childhood adiposity. Dairy products including whole milk are recognized to provide an important source of nutrition for toddlers, and they are a recommended component in the diets of toddlers as specified in the recent Dietary Guidelines for Americans (DGA) developed for toddlers and young children (USDA/HHS, 2020) and also guidance from the American Academy of Pediatrics (2020).

Consumption of Milk Fat by Infants in Infant Formula

The intended use of dry whole milk as an ingredient in infant formula will provide milk fat. The previous GRAS conclusion for use of up to 16 g dry whole milk in infant formula powder (GRN 980) notes that milk fat in the dry whole milk will account for 12% of the total fat in the formula as consumed. The use of anhydrous milk fat as a source of fat in cow milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants was concluded to be GRAS (GRN 898); the maximum use of anhydrous milk fat is 7.0% by weight of the fat blend in formulas containing up to 50% of energy as fat.

Milk fat has been used as a component of the fat blend in formulas examined in clinical trials, and results from these trials provide evidence to assess the suitability of the intended use of dry whole milk at a level of 22 g per 100 g infant formula powder. Four clinical trials in which a specified amount of cow's milk fat (2.8%, 20%, 48%, and 50% of fat) was included in infant formula were identified in the published literature (Breij *et al*., 2019; de Souza *et al*., 2018 and Leite *et al*., 2013; Manios *et al*., 2020 (two trials)); these trials are summarized in Appendix D. The source of milk fat (e.g., dry whole milk, cream, anhydrous milk) used in these formulations is not specified. All forms of milk fat provide a source of the fatty acids found in dry whole milk, though anhydrous milk fat provides little or no components located in the MFGM (Huppertz and Kelly, 2006). Results from these clinical interventions provide supportive evidence that milk fat as a component of the fat blend supports growth and is suitably tolerated by infants. These studies provide supporting evidence for the intended use of up to 22 g dry whole milk per 100 g infant formula powder, which accounts for 21% of total fat as milk fat based on representative product data.

GRAS Criteria

The regulatory framework for determining whether the use of a substance in food for animals can be considered GRAS in accordance with section 201(s) of the Federal Food, Drug, and Cosmetic Act ("the Act"), is set forth at 21 CFR §170.30:

> General recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.
>
> General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food

> additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data information.

In the preamble to the final rule for GRAS notices, FDA stated that a GRAS conclusion, based on scientific procedures may be supported by scientific data (such as human, animal, analytical or other scientific studies), information, methods and principles, published or unpublished, appropriate to establish the safety of a substance under the conditions of intended use. The safety standard requires a reasonable certainty of no harm under the conditions of intended use of the substance. To be eligible for a GRAS conclusion based on scientific procedures, there must be evidence of a consensus among qualified experts that the proposed use is safe and the pivotal data and information supporting the safety of the ingredient's intended use must be publicly available.

Safety Assessment

The substance that is the subject of this GRAS notice is the use of dry whole milk, when added at a maximum use level of 22 g per 100 g infant formula powder, as an ingredient in Nara Organics milk-based, non-exempt infant formula suitable as the sole source of nutrition from the first day of life for healthy term infants.

Safety Conclusion

The use of dry whole milk was previously concluded to be safe for the intended use as an ingredient at a level of 16 g per 100 g infant formula powder; we concur with that conclusion. The intended use of dry whole milk in this notice, at a maximum level of 22 g per 100 g infant formula powder, represents a modest increase in the intended use level of dry whole milk as an ingredient in infant formula powder, and a similar approach can be employed to evaluate the safety of the intended use.

The dry whole milk that is the subject of this notice is prepared from Grade "A" milk meeting specifications that ensure its safety as a food ingredient in the diet of infants. Based on the typical concentration of macronutrients in dry whole milk, the intended use of dry whole milk in the infant formula, and the total nutrient profile of the infant formula, the dry whole milk ingredient will contribute a portion of the formula's total protein (49%), total fat (21%), and total carbohydrate (16%).

Milk and milk products have a long history of use in the U.S. food supply, including consumption by infants and toddlers in the transition from a diet of exclusive human milk and/or formula, to foods. Milk, specifically whole milk and dry whole milk, are among these milk

products that have been consumed with no adverse effects attributable to the milk other than the well documented occurrence of allergic reactions in susceptible individuals (Abrams and Sicherer, 2021)**.**

Key physico-chemical similarities and differences between unmodified milk, dry whole milk, and nonfat dry milk arising from processing were discussed; these differences have no effect on the safety profile of the various forms of milk. The use of dry whole milk is not fundamentally different from the current use of the widely used nonfat dry milk and whey powder ingredients in infant formula. These ingredients are regarded as safe.

Published clinical studies of infants consuming whole milk support the safety of whole milk as a component of the diet (e.g., Alarcon *et al*., 1991; Brown *et al*., 1991; Hjelt *et al*., 1989; Isoulauri *et al*., 1986; Larnkjær *et al*., 2009; Stekel *et al*., 1988). Potential concerns with the consumption of fluid whole milk as a sole source of nutrition (e.g., potential nutrient deficiency, potential renal solute load; fat absorption) have been raised in the literature. However, the intended use of dry whole milk is as an ingredient in infant formula (a complex food matrix) and therefore provides only a portion of nutrients in the total formula. Thus, the intended use of dry whole milk does not present the same concerns as the direct consumption of fluid milk.

The use of dry whole milk in infant formula will provide a source of constituents typically present in lower concentrations in formula, namely phospholipids and other lipids present in milk fat and not present in vegetable oils. The level of these components provided by the intended use of dry whole milk will result in levels similar to or well below mean concentrations reported in human milk as shown in Table 13 and Table 15, and thus are not a safety concern. Published and unpublished clinical studies in which dairy fat accounts for up to approximately half the fat in infant formula (Breij *et al*., 2019; De Souza *et al*., 2018; Leite *et al*., 2013; Manios *et al*., 2020; Schouten, 2013, as cited in GRN 898) provide supportive evidence that the level of milk fat provided by the intended use of dry whole milk does not present safety concerns. The use of commercially available infant formulas in markets such as Australia and the United Kingdom that contain dry whole milk as a source of nutrients in the formulation also provides corroborative support regarding the safety of dry whole milk as an ingredient.

Conclusion Regarding Safety and General Recognition of Safety

General recognition of safety through scientific procedures requires common knowledge throughout the scientific community knowledgeable about the safety of food ingredients, and that there is a reasonable certainty that a substance is not harmful under the intended conditions of use in foods. The aforementioned regulatory, scientific reviews, and compositional data related to the consumption and safety of dry whole milk have been published in the scientific

literature and, therefore, are generally available and generally known among the community of qualified food ingredient safety experts. Thus, there is broad-based and widely disseminated knowledge concerning dry whole milk. The data and publicly available information supporting the safety of the proposed use of dry whole milk, for the intended use in infant formula, are not only widely known and disseminated, but are also commonly accepted among qualified food safety experts. The proposed use of dry whole milk at a maximum concentration of 22 g per 100 g infant formula powder can be concluded to be safe and GRAS through scientific procedures.

Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the proposed use of dry whole milk in non-exempt infant formula, meeting appropriate specifications specified herein and used according to cGMP, is safe and GRAS based on scientific procedures, under the conditions of intended use in food.

Part 7. List of Supporting Data and Information in GRAS Notice

Abrams EM, Sicherer SH. Cow's milk allergy prevention. Ann Allergy Asthma Immunol. 2021 Jul;127(1):36-41. doi: 10.1016/j.anai.2021.01.007. Epub 2021 Jan 13.

Alarcon P, Montoya R, Perez F, Dongo JW, Peerson JM, Brown KH. Clinical trial of home available, mixed diets versus a lactose-free, soy-protein formula for the dietary management of acute childhood diarrhea. J Pediatr Gastroenterol Nutr. 1991 Feb;12(2):224-32. doi: 10.1097/00005176-199102000-00015.

American Academy of Pediatrics (AAP) Committee on Nutrition. Pediatric nutrition. 8th ed.. 2020, Itasca, IL: American Academy of Pediatrics.

Anater AS, Catellier DJ, Levine BA, Krotki KP, Jacquier EF, Eldridge AL, Bronstein KE, Harnack LJ, Lorenzana Peasley JM, Lutes AC. The Feeding Infants and Toddlers Study (FITS) 2016: Study Design and Methods. J Nutr. 2018 Sep 1;148(9S):1516S-1524S. doi: 10.1093/jn/nxy035.

Berger A, Fleith M, Crozier G. Nutritional implications of replacing bovine milk fat with vegetable oil in infant formulas. J Pediatr Gastroenterol Nutr. 2000 Feb;30(2):115-30. doi: 10.1097/00005176-200002000-00006.

Bonuck K, Avraham SB, Hearst M, Kahn R, Hyden C. Is overweight at 12 months associated with differences in eating behaviour or dietary intake among children selected for inappropriate bottle use?. Matern Child Nutr. 2014 Apr;10(2):234-44. doi: 10.1111/mcn.12042. Epub 2013 Apr 5.

Breij LM, Abrahamse-Berkeveld M, Vandenplas Y, Jespers SNJ, de Mol AC, Khoo PC, Kalenga M, Peeters S, van Beek RHT, Norbruis OF, Schoen S, Acton D, Hokken-Koelega ACS; Mercurius Study Group. An infant formula with large, milk phospholipid-coated lipid droplets containing a mixture of dairy and vegetable lipids supports adequate growth and is well tolerated in healthy, term infants. Am J Clin Nutr. 2019 Mar 1;109(3):586-596. doi: 10.1093/ajcn/nqy322.

Brown KH, Perez F, Gastañaduy AS. Clinical trial of modified whole milk, lactose-hydrolyzed whole milk, or cereal-milk mixtures for the dietary management of acute childhood diarrhea. J Pediatr Gastroenterol Nutr. 1991 Apr;12(3):340-50. doi: 10.1097/00005176-199104000-00010.

Burd NA, Beals JW, Martinez IG, Salvador AF, Skinner SK. Food-First Approach to Enhance the Regulation of Post-exercise Skeletal Muscle Protein Synthesis and Remodeling. Sports Med. 2019 Feb;49(Suppl 1):59-68. doi: 10.1007/s40279-018-1009-y.

ByHeart. Generally Recognized as Safe (GRAS) Determination for the Intended Use of Dry Whole Milk in Nonexempt Infant Formula. GRAS Notice. November 2020, filed as GRN 980. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=980&sort=GRN_No&order=DESC&startrow=1&type=basic&search=980

Centers for Disease Control and Prevention National Health and Nutrition Examination Survey. 2021; https://www.cdc.gov/nchs/nhanes/index.htm. Accessed September 15, 2020.

Chardigny JM, Wolff RL, Mager E, Sébédio JL, Martine L, Juanéda P. Trans mono- and polyunsaturated fatty acids in human milk. Eur J Clin Nutr. 1995 Jul;49(7):523-31.

Claumarchirant L, Matencio E, Sanchez-Siles LM, Alegría A, Lagarda MJ. Sterol Composition in Infant Formulas and Estimated Intake. J Agric Food Chem. 2015 Aug 19;63(32):7245-51. doi: 10.1021/acs.jafc.5b02647. Epub 2015 Aug 11.

Codex. Code of hygienic practice for powdered infant formulae for infants and young children (CAC/RCP 66 – 2008); Adopted in 2008, Annex II adopted in 2009. http://www.fao.org/fao-who-codexalimentarius/codex-texts/codes-of-practice/en/

Contarini G, Povolo M. Phospholipids in milk fat: composition, biological and technological significance, and analytical strategies. Int J Mol Sci. 2013 Jan 29;14(2):2808-31. doi: 10.3390/ijms14022808.

Corkins KG, Shurley T. What's in the Bottle? A Review of Infant Formulas. Nutr Clin Pract. 2016 Dec;31(6):723-729. doi: 10.1177/0884533616669362. Epub 2016 Sep 25.

de Souza CO, Leite MEQ, Lasekan J, Baggs G, Pinho LS, Druzian JI, Ribeiro TCM, Mattos ÂP, Menezes-Filho JA, Costa-Ribeiro H. Milk protein-based formulas containing different oils affect fatty acids balance in term infants: A randomized blinded crossover clinical trial. Lipids Health Dis. 2017 Apr 14;16(1):78. doi: 10.1186/s12944-017-0457-y.

Fomon S. Infant feeding in the 20th century: formula and beikost. J Nutr. 2001 Feb;131(2):409S-20S. doi: 10.1093/jn/131.2.409S.

Fomon SJ, Ziegler EE, Nelson SE, Edwards BB. Cow milk feeding in infancy: gastrointestinal blood loss and iron nutritional status. J Pediatr. 1981 Apr;98(4):540-5. doi: 10.1016/s0022-3476(81)80756-1.

Fomon SJ, Ziegler EE, Thomas LN, Jensen RL, Filer LJ Jr. Excretion of fat by normal full-term infants fed various milks and formulas. Am J Clin Nutr. 1970 Oct;23(10):1299-313. doi: 10.1093/ajcn/23.10.1299.

Fomon, SJ. Nutrition of Normal Infants. 1993. Mosby-Year Book, Inc.: St. Louis, MO.

Food and Agriculture Organization (FAO) of the United Nations. Dietary protein quality evaluation in human nutrition: Report of an FAO Expert Consultation, FAO Food and Nutrition Paper 92. 2013; Rome.

Gallier S, Tolenaars L, Prosser C. Whole Goat Milk as a Source of Fat and Milk Fat Globule Membrane in Infant Formula. Nutrients. 2020 Nov 13;12(11):3486. doi: 10.3390/nu12113486.

Glew RH, Wold RS, Corl B, Calvin CD, Vanderjagt DJ. Low docosahexaenoic acid in the diet and milk of American Indian women in New Mexico. J Am Diet Assoc. 2011 May;111(5):744-8. doi: 10.1016/j.jada.2011.02.001.

Grimes CA, Szymlek-Gay EA, Campbell KJ, Nicklas TA. Food Sources of Total Energy and Nutrients among U.S. Infants and Toddlers: National Health and Nutrition Examination Survey 2005-2012. Nutrients. 2015 Aug 14;7(8):6797-836. doi: 10.3390/nu7085310.

Hageman JHJ , Keijer J , Dalsgaard TK , Zeper LW , Carrière F , Feitsma AL , Nieuwenhuizen AG . Free fatty acid release from vegetable and bovine milk fat-based infant formulas and human milk during two-phase in vitro digestion. Food Funct. 2019a Apr 17;10(4):2102-2113. doi: 10.1039/c8fo01940a.

Hageman JHJ, Danielsen M, Nieuwenhuizen AG, Feitsma AL, Dalsgaard TK. Comparison of bovine milk fat and vegetable fat for infant formula: Implications for infant health. Int Dairy J. 2019c; 92:37e49. doi: 10.1016/j.idairyj.2019.01.005.

Hageman JHJ, Keijer J, Dalsgaard TK, Zeper LW, Carrière F, Feitsma AL, Nieuwenhuizen AG. Correction: Free fatty acid release from vegetable and bovine milk fat-based infant formulas and human milk during two-phase in vitro digestion. Food Funct. 2019b May 22;10(5):3018-3020. doi: 10.1039/c9fo90021g.

Hertrampf E, Olivares M, Walter T, Pizarro F, Heresi G, Llaguno S, Vega V, Cayazzo M, Chadud P. [Iron-deficiency anemia in the nursing infant: its elimination with iron-fortified milk]. Rev Med Chil. 1990 Dec;118(12):1330-7.

Hjelt K, Paerregaard A, Petersen W, Christiansen L, Krasilnikoff PA. Rapid versus gradual refeeding in acute gastroenteritis in childhood: energy intake and weight gain. J Pediatr Gastroenterol Nutr. 1989 Jan;8(1):75-80. doi: 10.1097/00005176-198901000-00014.

Hogan Lovells. GRAS Notice for the Use of Anhydrous Milk Fat (AMF) in Exempt Infant Formula. GRAS Notice. November 2019, filed as GRN 898. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices&id=898&sort=GRN_No&order=DESC&startrow=1&type=basic&search=898

Houghton LA, Gray AR, Szymlek-Gay EA, Heath AL, Ferguson EL. Vitamin D-fortified milk achieves the targeted serum 25-hydroxyvitamin D concentration without affecting that of parathyroid hormone in New Zealand toddlers. J Nutr. 2011 Oct;141(10):1840-6. doi: 10.3945/jn.111.145052. Epub 2011 Aug 10.

Huppertz T, Kelly AL. Physical Chemistry of Milk Fat Globules. In: Advanced Dairy Chemistry Vol 2 Lipids. Eds: Fox PF, McSweeney PLH. 2006. pp 1-42. Springer: US.

Innis SM. Dietary triacylglycerol structure and its role in infant nutrition. Adv Nutr. 2011 May;2(3):275-83. doi: 10.3945/an.111.000448. Epub 2011 Apr 30.

Institute of Medicine (IOM) US Committee on the Evaluation of the Addition of Ingredients New to Infant Formula. Infant Formula: Evaluating the Safety of New Ingredients. Washington (DC): National Academies Press (US); 2004.

Institute of Medicine (IOM). Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. 2005; Washington, DC: The National Academies Press. https://doi.org/10.17226/10490.

Isolauri E, Vesikari T, Saha P, Viander M. Milk versus no milk in rapid refeeding after acute gastroenteritis. J Pediatr Gastroenterol Nutr. 1986 Mar-Apr;5(2):254-61.

Jensen RG, Ferris AM, Lammi-Keefe CJ. The composition of milk fat. J Dairy Sci. 1991 Sep;74(9):3228-43. doi: 10.3168/jds.S0022-0302(91)78509-3.

Jensen RG, Jensen GL. Specialty lipids for infant nutrition. I. Milks and formulas. J Pediatr Gastroenterol Nutr. 1992 Oct;15(3):232-45. doi: 10.1097/00005176-199210000-00002.

Jiang T, Jeter JM, Nelson SE, Ziegler EE. Intestinal blood loss during cow milk feeding in older infants: quantitative measurements. Arch Pediatr Adolesc Med. 2000 Jul;154(7):673-8. doi: 10.1001/archpedi.154.7.673.

Kay MC, Welker EB, Jacquier EF, Story MT. Beverage Consumption Patterns among Infants and Young Children (0⁻47.9 Months): Data from the Feeding Infants and Toddlers Study, 2016. Nutrients. 2018 Jun 26;10(7):825. doi: 10.3390/nu10070825.

Kien CL. Digestion, absorption, and fermentation of carbohydrates in the newborn. Clin Perinatol. 1996 Jun;23(2):211-28.

Koletzko B. Human Milk Lipids. Ann Nutr Metab. 2016;69 Suppl 2:28-40. doi: 10.1159/000452819. Epub 2017 Jan 20.

Larnkjaer A, Hoppe C, Mølgaard C, Michaelsen KF. The effects of whole milk and infant formula on growth and IGF-I in late infancy. Eur J Clin Nutr. 2009 Aug;63(8):956-63. doi: 10.1038/ejcn.2008.80. Epub 2009 Jan 28.

Le Huërou-Luron I, Bouzerzour K, Ferret-Bernard S, Ménard O, Le Normand L, Perrier C, Le Bourgot C, Jardin J, Bourlieu C, Carton T, Le Ruyet P, Cuinet I, Bonhomme C, Dupont D. A mixture of milk and vegetable lipids in infant formula changes gut digestion, mucosal immunity and microbiota composition in neonatal piglets. Eur J Nutr. 2018 Mar;57(2):463-476. doi: 10.1007/s00394-016-1329-3. Epub 2016 Oct 15.

Leite ME, Lasekan J, Baggs G, Ribeiro T, Menezes-Filho J, Pontes M, Druzian J, Barreto DL, de Souza CO, Mattos Â, Costa-Ribeiro H Jr. Calcium and fat metabolic balance, and gastrointestinal tolerance in term infants fed milk-based formulas with and without palm olein and palm kernel oils: a randomized blinded crossover study. BMC Pediatr. 2013 Dec 24;13:215. doi: 10.1186/1471-2431-13-215.

Li S, Ye A, Singh H. Impacts of heat-induced changes on milk protein digestibility: A review. International Dairy Journal. 2021;123:105160. doi: 10.1016/j.idairyj.2021.105160.

Life Sciences Research Office (LSRO) Expert Panel Report Assessment of nutrient requirements for infant formulas. J Nutr. 1998 Nov;128(11 Suppl):i-iv, 2059S-2293S.

Linn, JG. Factors Affecting the Composition of Milk from Dairy Cows. In: Designing Foods: Animal Product Options in the Marketplace.. National Research Council (US) Committee on Technological Options to Improve the Nutritional Attributes of Animal Products. Washington (DC): National Academies Press (US); 1988.

Liu L, Zhang X, Liu Y, Wang L, Li X. Simulated In Vitro Infant Gastrointestinal Digestion of Infant Formulas Containing Different Fat Sources and Human Milk: Differences in Lipid Profiling and Free Fatty Acid Release. J Agric Food Chem. 2021 Jun 23;69(24):6799-6809. doi: 10.1021/acs.jafc.1c01760. Epub 2021 Jun 14.

Lloyd MA, Hess SJ, Drake MA. Effect of nitrogen flushing and storage temperature on flavor and shelf-life of whole milk powder. J Dairy Sci. 2009 Jun;92(6):2409-22. doi: 10.3168/jds.2008-1714.

Manios Y, Karaglani E, Thijs-Verhoeven I, Vlachopapadopoulou E, Papazoglou A, Maragoudaki E, Manikas Z, Kampani TM, Christaki I, Vonk MM, Bos R, Parikh P. Effect of milk fat-based infant formulae on stool fatty acid soaps and calcium excretion in healthy term infants: two double-blind randomised cross-over trials. BMC Nutr. 2020 Sep 14;6:46. doi: 10.1186/s40795-020-00365-4. eCollection 2020.

Martin CR, Ling PR, Blackburn GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. Nutrients. 2016 May 11;8(5):279. doi: 10.3390/nu8050279.

Martysiak-Żurowska D, Kiełbratowska B, Szlagatys-Sidorkiewicz A. The content of conjugated linoleic acid and vaccenic acid in the breast milk of women from Gdansk and the surrounding district, as well as in, infant formulas and follow-up formulas. nutritional recommendation for nursing women. Dev Period Med. 2018;22(2):128-134.

Maulen-Radovan I, Villagómez S, Soler E, Villicaña R, Hernández-Ronquillo L, Rosado JL. [Nutritional impact of whole milk supplemented with vitamins and minerals in children]. Salud Publica Mex. 1999 Sep-Oct;41(5):389-96.

McGuire MK, Park Y, Behre RA, Harrison LY, Shultz TD, McGuire MA. Conjugated linoleic acid concentrations of human milk and infant formula. Nutr Res. 1997;17(8):1277-83.

Mohan MS, O'Callaghan TF, Kelly P, Hogan SA. Milk fat: opportunities, challenges and innovation. Crit Rev Food Sci Nutr. 2020 Jul 10:1-33. doi: 10.1080/10408398.2020.1778631. Online ahead of print.

Mosley EE, Wright AL, McGuire MK, McGuire MA. trans Fatty acids in milk produced by women in the United States. Am J Clin Nutr. 2005 Dec;82(6):1292-7. doi: 10.1093/ajcn/82.6.1292.

Mueller A, Thijs C, Rist L, Simões-Wüst AP, Huber M, Steinhart H. Trans fatty acids in human milk are an indicator of different maternal dietary sources containing trans fatty acids. Lipids. 2010 Mar;45(3):245-51. doi: 10.1007/s11745-010-3390-7. Epub 2010 Feb 11.

Penrod JC, Anderson K, Acosta PB. Impact on iron status of introducing cow's milk in the second six months of life. J Pediatr Gastroenterol Nutr. 1990 May;10(4):462-7. doi: 10.1097/00005176-199005000-00008.

Perusko M, van Roest M, Stanic-Vucinic D, Simons PJ, Pieters RHH, Cirkovic Velickovic T, Smit JJ. Glycation of the Major Milk Allergen β-Lactoglobulin Changes Its Allergenicity by Alterations in Cellular Uptake and Degradation. Mol Nutr Food Res. 2018 Sep;62(17):e1800341. doi: 10.1002/mnfr.201800341. Epub 2018 Jul 29.

Prentice PM, Schoemaker MH, Vervoort J, Hettinga K, Lambers TT, van Tol EAF, Acerini CL, Olga L, Petry CJ, Hughes IA, Koulman A, Ong KK, Dunger DB. Human Milk Short-Chain Fatty Acid Composition is Associated with Adiposity Outcomes in Infants. J Nutr. 2019 May 1;149(5):716-722. doi: 10.1093/jn/nxy320.

Ratnayake WN, Swist E, Zoka R, Gagnon C, Lillycrop W, Pantazapoulos P. Mandatory trans fat labeling regulations and nationwide product reformulations to reduce trans fatty acid content in foods contributed to lowered concentrations of trans fat in Canadian women's breast milk samples collected in 2009-2011. Am J Clin Nutr. 2014 Oct;100(4):1036-40. doi: 10.3945/ajcn.113.078352. Epub 2014 Jul 23.

Rodríguez-Alcalá LM, Calvo MV, Fontecha J, Alonso L. Alterations in the Fatty Acid Composition in Infant Formulas and ω3-PUFA Enriched UHT Milk during Storage. Foods. 2019 May 13;8(5):163. doi: 10.3390/foods8050163.

Rossen LM, Simon AE, Herrick KA. Types of Infant Formulas Consumed in the United States. Clin Pediatr (Phila). 2016 Mar;55(3):278-85. doi: 10.1177/0009922815591881. Epub 2015 Jul 6.

Rudloff S, Lönnerdal B. Solubility and digestibility of milk proteins in infant formulas exposed to different heat treatments. J Pediatr Gastroenterol Nutr. 1992 Jul;15(1):25-33. doi: 10.1097/00005176-199207000-00005.

Santillo A, Figliola L, Ciliberti MG, Caroprese M, Marino R, Albenzio M. Focusing on fatty acid profile in milk from different species after in vitro digestion. J Dairy Res. 2018 May;85(2):257-262. doi: 10.1017/S0022029918000274.

Sarwar G, Peace RW, Botting HG. Differences in protein digestibility and quality of liquid concentrate and powder forms of milk-based infant formulas fed to rats. Am J Clin Nutr. 1989 May;49(5):806-13. doi: 10.1093/ajcn/49.5.806.

Soga S, Ota N, Shimotoyodome A. 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. 2015 Aug 25;14:85. doi: 10.1186/s12937-015-0073-5.

Stekel A, F Pizarro, M Olivares, P Chadud, S Llaguno, M Cayazzo, E Hertrampf, T Walter Prevention of iron deficiency by milk fortification. III. Effectiveness under the usual operational conditions of a nation-wide food program. Nutr Rep Int. 1988; 38:1119-1128.

Sun C, Zou X, Yao Y, Jin J, Xia Y, Huang J, Jin Q, Wang X. Evaluation of fatty acid composition in commercial infant formulas on the Chinese market: A comparative study based on fat source and stage. Int Dairy J. 2016; 63:42-51.

Svahn JC, Feldl F, Räihä NC, Koletzko B, Axelsson IE. Fatty acid content of plasma lipid fractions, blood lipids, and apolipoproteins in children fed milk products containing different quantity and quality of fat. J Pediatr Gastroenterol Nutr. 2000 Aug;31(2):152-61. doi: 10.1097/00005176-200008000-00012.

Thomas DW, McGilligan KM, Carlson M, Azen SP, Eisenberg LD, Lieberman HM, Rissman EM. Fecal alpha 1-antitrypsin and hemoglobin excretion in healthy human milk-, formula-, or cow's milk-fed infants. Pediatrics. 1986 Aug;78(2):305-12.

Torres MA, Sato K, Lobo NF, de Souza Queiroz S. [The effect of the use of milk fortified with iron and vitamin C on hemoglobin levels and nutritional status of children under 2]. Rev Saude Publica. 1995 Aug;29(4):301-7. doi: 10.1590/s0034-89101995000400008.

U.S. Department of Agriculture and U.S. Department of Health and Human Services (USDA/HHS). Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov.

U.S. Department of Agriculture. FoodData Central; Milk, dry, not reconstituted, whole; FDC ID: 1097874. https://fdc.nal.usda.gov/.

U.S. Department of Agriculture. FoodData Central; Milk, dry, whole, without added vitamin D; FDC ID: 173454, NDB Number:1212. https://fdc.nal.usda.gov/. Accessed July 24, 2021.

U.S. Food and Drug Administration (FDA). GRAS Notice GRN 898 Agency Response Letter.. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&startrow=1&type=basic&search=898

U.S. Food and Drug Administration (FDA). GRAS Notice GRN 980 Agency Response Letter.. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=980&sort=GRN_No&order=DESC&startrow=1&type=basic&search=980

van der Gaag E, Brandsema R, Nobbenhuis R, van der Palen J, Hummel T. Influence of Dietary Advice Including Green Vegetables, Beef, and Whole Dairy Products on Recurrent Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial. Nutrients. 2020 Jan 20;12(1):272. doi: 10.3390/nu12010272.

van der Gaag EJ, Forbes K. The Immunomodulating Effect of a Diet Consisting of Green Vegetables, Beef, Whole Milk and Full-Fat Butter for Children with Non-Specific Elevated IgE. Int J Vitam Nutr Res. 2014;84(5-6):310-9. doi: 10.1024/0300-9831/a000217.

van der Gaag EJ, Wieffer R, van der Kraats J. Advising Consumption of Green Vegetables, Beef, and Full-Fat Dairy Products Has No Adverse Effects on the Lipid Profiles in Children. Nutrients. 2017 May 19;9(5):518. doi: 10.3390/nu9050518.

van Lieshout GAA, Lambers TT, Bragt MCE, Hettinga KA. How processing may affect milk protein digestion and overall physiological outcomes: A systematic review. Crit Rev Food Sci Nutr. 2020;60(14):2422-2445. doi: 10.1080/10408398.2019.1646703. Epub 2019 Aug 22.

Vanderhout SM, Aglipay M, Torabi N, Jüni P, da Costa BR, Birken CS, O'Connor DL, Thorpe KE, Maguire JL. Whole milk compared with reduced-fat milk and childhood overweight: a systematic review and meta-analysis. Am J Clin Nutr. 2020 Feb 1;111(2):266-279. doi: 10.1093/ajcn/nqz276.

Vanderhout SM, Birken CS, Parkin PC, Lebovic G, Chen Y, O'Connor DL, Maguire JL; TARGet Kids! Collaboration. Relation between milk-fat percentage, vitamin D, and BMI z score

in early childhood. Am J Clin Nutr. 2016 Dec;104(6):1657-1664. doi: 10.3945/ajcn.116.139675. Epub 2016 Nov 16.

Vanderhout SM, Birken CS, Parkin PC, Lebovic G, Chen Y, O'Connor DL, Maguire JL; TARGetKids! Collaboration. Higher milk fat content is associated with higher 25-hydroxyvitamin D concentration in early childhood. Appl Physiol Nutr Metab. 2016 May;41(5):516-21. doi: 10.1139/apnm-2015-0671. Epub 2016 Jan 13.

Wada Y, Lönnerdal B. Effects of different industrial heating processes of milk on site-specific protein modifications and their relationship to in vitro and in vivo digestibility. J Agric Food Chem. 2014 May 7;62(18):4175-85. doi: 10.1021/jf501617s. Epub 2014 Apr 24.

Wan ZX, Wang XL, Xu L, Geng Q, Zhang Y. Lipid content and fatty acids composition of mature human milk in rural North China. Br J Nutr. 2010 Mar;103(6):913-6. doi: 10.1017/S0007114509992455. Epub 2009 Oct 14.

Wilson JF, Lahey ME, Heiner DC. Studies on iron metabolism. V. Further observations on cow's milk-induced gastrointestinal bleeding in infants with iron-deficiency anemia. J Pediatr. 1974 Mar;84(3):335-44. doi: 10.1016/s0022-3476(74)80713-4.

Wong VCH, Maguire JL, Omand JA, Dai DWH, Lebovic G, Parkin PC, O'Connor DL, Birken CS; TARGet Kids! Collaboration. A Positive Association Between Dietary Intake of Higher Cow's Milk-Fat Percentage and Non-High-Density Lipoprotein Cholesterol in Young Children. J Pediatr. 2019 Aug;211:105-111.e2. doi: 10.1016/j.jpeds.2019.03.047. Epub 2019 May 17.

Woodruff CW, Wright SW, Wright RP. The role of fresh cow's milk in iron deficiency. II. Comparison of fresh cow's milk with a prepared formula. Am J Dis Child. 1972 Jul;124(1):26-30. doi: 10.1001/archpedi.1972.02110130028004.

Yuhas R, Pramuk K, Lien EL. Human milk fatty acid composition from nine countries varies most in DHA. Lipids. 2006 Sep;41(9):851-8. doi: 10.1007/s11745-006-5040-7.

Ziegler EE, Fomon SJ, Nelson SE, Rebouche CJ, Edwards BB, Rogers RR, Lehman LJ. Cow milk feeding in infancy: further observations on blood loss from the gastrointestinal tract. J Pediatr. 1990 Jan;116(1):11-8. doi: 10.1016/s0022-3476(05)90003-6.

Ziegler EE, Fomon SJ. Potential renal solute load of infant formulas. J Nutr. 1989 Dec;119(12 Suppl):1785-8. doi: 10.1093/jn/119.12_Suppl.1785.

Ziegler EE, Jiang T, Romero E, Vinco A, Frantz JA, Nelson SE. Cow's milk and intestinal blood loss in late infancy. J Pediatr. 1999 Dec;135(6):720-6. doi: 10.1016/s0022-3476(99)70091-0.

Ziegler EE. Consumption of cow's milk as a cause of iron deficiency in infants and toddlers. Nutr Rev. 2011 Nov;69 Suppl 1:S37-42. doi: 10.1111/j.1753-4887.2011.00431.x.

Appendices

Appendix A. Supplier PMO Statement

[redacted]

August 18, 2021

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). [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 subsection 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 subsection 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.
- 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 subsection 205.670 both require periodic pesticide testing at the producer level and farm level. [redacted] and its affiliate farms all abide and meet the requirement outlined in the regulations.
    - In addition, organic farmers are greatly limited in the type of pesticides allowed for use by the NOP. Section 7 subsection 205.601-205.604 describe the allowed and prohibited substances.
    - Any additional testing outside the Grade "A" PMO or the NOP shall be completed by the customer.

Please do not hesitate to contact me with further questions.

[redacted]

[redacted]

Appendix B. WWEIA/NHANES 2011-2018 infant formula food codes included in the analysis

Food code	Food description
11710000	Infant formula, NFS
11710051	Infant formula, ready-to-feed (Similac Expert Care Alimentum)
11710053	Infant formula, powder, made with water, NFS (Similac Expert Care Alimentum)
11710054	Infant formula, powder, made with tap water (Similac Expert Care Alimentum)
11710055	Infant formula, powder, made with plain bottled water (Similac Expert Care Alimentum)
11710056	Infant formula, powder, made with baby water (Similac Expert Care Alimentum)
11710350	Infant formula, NS as to form (Similac Advance)
11710351	Infant formula, ready-to-feed (Similac Advance)
11710353	Infant formula, powder, made with water, NFS (Similac Advance)
11710354	Infant formula, liquid concentrate, made with tap water (Similac Advance)
11710355	Infant formula, liquid concentrate, made with plain bottled water (Similac Advance)
11710356	Infant formula, liquid concentrate, made with baby water (Similac Advance)
11710357	Infant formula, powder, made with tap water (Similac Advance)
11710358	Infant formula, powder, made with plain bottled water (Similac Advance)
11710359	Infant formula, powder, made with baby water (Similac Advance)
11710367	Infant formula, powder, made with tap water (Similac Advance Organic)
11710369	Infant formula, powder, made with baby water (Similac Advance Organic)
11710370	Infant formula, NS as to form (Similac Sensitive)
11710371	Infant formula, ready-to-feed (Similac Sensitive)
11710373	Infant formula, powder, made with water, NFS (Similac Sensitive)
11710374	Infant formula, liquid concentrate, made with tap water (Similac Sensitive)
11710376	Infant formula, liquid concentrate, made with baby water (Similac Sensitive)
11710377	Infant formula, powder, made with tap water (Similac Sensitive)
11710378	Infant formula, powder, made with plain bottled water (Similac Sensitive)
11710379	Infant formula, powder, made with baby water (Similac Sensitive)
11710380	Infant formula, NS as to form (Similac for Spit-Up)
11710381	Infant formula, ready-to-feed (Similac for Spit-Up)
11710383	Infant formula, powder, made with water, NFS (Similac for Spit-Up)
11710387	Similac Sensitive for Spit-Up, infant formula, prepared from powder, made with tap water
11710388	Similac Sensitive for Spit-Up, infant formula, prepared from powder, made with plain bottled water
11710389	Similac Sensitive for Spit-Up, infant formula, prepared from powder, made with baby water
11710480	Infant formula, NS as to form (Similac Go and Grow)
11710481	Infant formula, powder, made with water, NFS (Similac Go and Grow)
11710621	Infant formula, ready-to-feed (Enfamil Newborn)
11710626	Infant formula, powder, made with water, NFS (Enfamil Newborn)
11710627	Infant formula, powder, made with tap water (Enfamil Newborn)
11710628	Infant formula, powder, made with plain bottled water (Enfamil Newborn)
11710629	Infant formula, powder, made with baby water (Enfamil Newborn)

Food code	Food description
11710630	Infant formula, NS as to form (Enfamil Infant)
11710631	Infant formula, ready-to-feed (Enfamil Infant)
11710633	Infant formula, liquid concentrate, made with tap water (Enfamil Infant)
11710634	Infant formula, liquid concentrate, made with plain bottled water (Enfamil Infant)
11710635	Infant formula, liquid concentrate, made with baby water (Enfamil Infant)
11710637	Infant formula, powder, made with tap water (Enfamil Infant)
11710638	Infant formula, powder, made with plain bottled water (Enfamil Infant)
11710639	Infant formula, powder, made with baby water (Enfamil Infant)
11710644	Enfamil PREMIUM LIPIL, infant formula, prepared from liquid concentrate, made with tap water
11710645	Enfamil PREMIUM LIPIL, infant formula, prepared from liquid concentrate, made with plain bottled water
11710646	Enfamil PREMIUM LIPIL, infant formula, prepared from liquid concentrate, made with baby water
11710654	Enfamil LIPIL, infant formula, prepared from liquid concentrate, made with tap water
11710656	Enfamil LIPIL, infant formula, prepared from liquid concentrate, made with baby water
11710660	Infant formula, NS as to form (Enfamil A.R.)
11710664	Infant formula, powder, made with tap water (Enfamil A.R.)
11710668	Infant formula, powder, made with plain bottled water (Enfamil A.R.)
11710669	Infant formula, powder, made with baby water (Enfamil A.R.)
11710671	Infant formula, ready-to-feed (Enfamil Gentlease)
11710677	Infant formula, powder, made with tap water (Enfamil Gentlease)
11710678	Infant formula, powder, made with plain bottled water (Enfamil Gentlease)
11710679	Infant formula, powder, made with baby water (Enfamil Gentlease)
11710681	Infant formula, ready-to-feed (Enfamil Enfragrow Toddler Transitions)
11710687	Infant formula, powder, made with tap water (Enfamil Enfagrow Toddler Transitions)
11710688	Infant formula, powder, made with plain bottled water (Enfamil Enfagrow Toddler Transitions)
11710689	Infant formula, powder, made with baby water (Enfamil Enfagrow Toddler Transitions)
11710690	Infant formula, NS as to form (Enfamil Enfagrow Toddler Transitions Gentlease)
11710697	Infant formula, powder, made with tap water (Enfamil Enfagrow Toddler Transitions Gentlease)
11710698	Infant formula, powder, made with plain bottled water (Enfamil Enfagrow Toddler Transitions Gentlease)
11710699	Infant formula, powder, made with baby water (Enfamil Enfagrow Toddler Transitions Gentlease)
11710910	Infant formula, NS as to form (Gerber Good Start Gentle)
11710911	Infant formula, ready-to-feed (Gerber Good Start Gentle)
11710913	Infant formula, powder, made with water, NFS (Gerber Good Start Gentle)
11710914	Infant formula, liquid concentrate, made with tap water (Gerber Good Start Gentle)
11710916	Infant formula, liquid concentrate, made with baby water (Gerber Good Start Gentle)
11710917	Infant formula, powder, made with tap water (Gerber Good Start Gentle)
11710918	Infant formula, powder, made with plain bottled water (Gerber Good Start Gentle)
11710919	Infant formula, powder, made with baby water (Gerber Good Start Gentle)
11710920	Infant formula, NS as to form (Gerber Good Start Protect)

Food code	Food description
11710927	Infant formula, powder, made with tap water (Gerber Good Start Protect)
11710928	Infant formula, powder, made with plain bottled water (Gerber Good Start Protect)
11710929	Infant formula, powder, made with baby water (Gerber Good Start Protect)
11710962	Infant formula, powder, made with water, NFS (Store Brand)
11710963	Infant formula, ready-to-feed (Store Brand)
11710964	Infant formula, liquid concentrate, made with tap water (Store Brand)
11710966	Infant formula, liquid concentrate, made with baby water (Store Brand)
11710967	Infant formula, powder, made with tap water (Store Brand)
11710968	Infant formula, powder, made with plain bottled water (Store Brand)
11710969	Infant formula, powder, made with baby water (Store Brand)
11720311	Infant formula, ready-to-feed (Enfamil ProSobee)
11720316	Infant formula, liquid concentrate, made with baby water (Enfamil ProSobee)
11720317	Infant formula, powder, made with tap water (Enfamil ProSobee)
11720318	Infant formula, powder, made with plain bottled water (Enfamil ProSobee)
11720319	Infant formula, powder, made with baby water (Enfamil ProSobee)
11720411	Infant formula, ready-to-feed (Similac Isomil Soy)
11720414	Infant formula, liquid concentrate, made with tap water (Similac Isomil Soy)
11720416	Infant formula, liquid concentrate, made with baby water (Similac Isomil Soy)
11720417	Infant formula, powder, made with tap water (Similac Isomil Soy)
11720418	Infant formula, powder, made with plain bottled water (Similac Isomil Soy)
11720419	Infant formula, powder, made with baby water (Similac Isomil Soy)
11720430	Infant formula, NS as to form (Similac Expert Care for Diarrhea)
11720431	Infant formula, ready-to-feed (Similac Expert Care for Diarrhea)
11720615	Infant formula, liquid concentrate, made with plain bottled water (Gerber Good Start Soy)
11720617	Infant formula, powder, made with tap water (Gerber Good Start Soy)
11720618	Infant formula, powder, made with plain bottled water (Gerber Good Start Soy)
11720619	Infant formula, powder, made with baby water (Gerber Good Start Soy)
11720620	Infant formula, NS as to form (Gerber Graduates Soy)
11720807	Infant formula, powder, made with tap water (Store Brand Soy)
11720808	Infant formula, powder, made with plain bottled water (Store Brand Soy)
11720809	Infant formula, powder, made with baby water (Store Brand Soy)
11740317	Enfamil Nutramigen LIPIL, infant formula, prepared from powder, made with tap water
11740318	Enfamil Nutramigen LIPIL, infant formula, prepared from powder, made with plain bottled water
11740319	Enfamil Nutramigen LIPIL, infant formula, prepared from powder, made with baby water
11740323	Infant formula, powder, made with water, NFS (PurAmino)
11740400	Infant formula, NS as to form (Enfamil Pregestimil)
11740403	Infant formula, powder, made with water, NFS (Enfamil Pregestimil)
11740407	Enfmail Pregestimil LIPIL, infant formula, prepared from powder, made with tap water
11740520	Enfamil Premature LIPIL 20, with iron, infant formula, NS as to form

Appendix C. PubMed Literature Searches

No.	Search String	Hits	Date
1	Search: (bovine[tiab] OR cow[tiab] OR dairy[tiab]) AND ("milk fat" OR "milkfat" OR "whole milk" OR "butter fat" OR "butterfat" OR "milk powder" OR "evaporated milk" OR "condensed milk") AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn) Filters: English, Humans Sort by: Most Recent	197	6/2/2021
2	Search: (concentration OR absorption OR digestion) AND (sphingolipid[tiab] or phospholipid[tiab]) AND (infant OR newborn OR "breast milk" OR "human milk" OR breastmilk OR "breastfed" OR "breast fed") Filters: Humans, English, from 2011/1/1 - 3000/12/12 Sort by: Most Recent	74	6/2/2021
3	Search: ((fecal fat loss) OR (fat excretion)) AND infant AND milk Filters: Humans, English Sort by: Most Recent	66	6/2/2021
4	Search: review AND (cow OR bovine OR dairy) AND iron AND infant AND milk AND (Metabolism OR digestion OR excretion OR elimination) AND (Safe OR Risk OR Adverse OR Tolerance) Filters: Humans, English Sort by: Most Recent	24	6/2/2021
5	Search: ((bovine OR cow OR dairy) AND milk) AND (infant gut) AND (metabolism or absorption or digestion or excretion or bioavailability or elimination or immune) Filters: English, Humans Sort by: Most Recent	211	6/2/2021
6	Search: ((trans fat) OR trans-fat) OR (trans fatty OR (trans-fatty)) AND (infant OR newborn OR "breast milk" OR "human milk" OR breastmilk OR "breastfed" OR "breast fed") Filters: English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	27	6/2/2021
7	Search: "cholesterol"[tw] AND (infant[tw] OR newborn[tw] OR "breast milk"[tw] OR "human milk"[tw] OR breastmilk[tw] OR "breastfed"[tw] OR "breast fed"[tw]) AND (dietary OR intake OR consumption) Filters: Humans, English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	42	6/2/2021
8	Search: branched chain fatty acids AND (infant OR newborn OR "breast milk" OR "human milk" OR breastmilk OR "breastfed" OR "breast fed") Filters: English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	30	6/2/2021
9	Search: (vaccenic OR rumenic OR CLA OR "conjugated linoleic acid") AND (infant OR newborn OR "breast milk" OR "human milk" OR breastmilk OR "breastfed" OR "breast fed") Filters: English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	61	6/2/2021
10	Search: (odd chain fatty acid) AND (infant OR newborn OR "breast milk" OR "human milk" OR breastmilk OR "breastfed" OR "breast fed") Filters: English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	8	6/2/2021
11	Search: "Feeding Infants and Toddlers" Filters: English Sort by: Most Recent	5	6/2/2021
12	Search: "whole milk" AND (dry OR powder) AND (composition OR safety OR stability OR oxidation) Filters: English, from 2011/1/1 - 3000/12/12 Sort by: Most Recent	67	6/2/2021
13	Search: (bovine OR cow OR dairy) AND (fat OR lipid) AND (infant formula) Filters: English, from 2019/1/1 - 3000/12/12 Sort by: Most Recent	98	9/8/2021

Appendix D. Prospective Randomized Trials of Infants Consuming Whole Milk or Dairy Fat

Appendix D, Table 1. Prospective randomized trials of infants consuming whole cow's milk

Reference	Population	Intervention	Key Results
Alarcon et al., 1991	Population: 85 Peruvian infants and children, hospitalized for acute diarrhea Age range: 5-24 months, stratified into ages 5-6 months and 7-24 months Mean age: 11.9±4.2 months	Duration: 6 days Test material: 1) Mixture of dried whole milk, potato flour, carrot flour, sucrose & vegetable oil 2) Mixture of wheat flour, pea flour, carrot flour, sucrose, & vegetable oil 3) Soy-protein isolate, lactose-free formula Intake of test material: 110 kcal/kg bw/day Intake of whole milk powder (1st diet): 6.46 g No additional foods allowed	Key results: Children in all groups gained weight; no differences were observed in anthropometric status, energy intakes, energy absorption, nitrogen retention, or fecal output and no differences in treatment failure. Authors' conclusion: The " 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."
Brown *et al*., 1991	Population: 116 Peruvian male infants and toddlers with acute diarrhea Age range: 3-24 months Mean age: 12.5±6.1 months	Duration: 6 days Test material: 1) Modified whole milk & wheat noodles with vegetable oil 2) Lactose-hydrolyzed whole milk & wheat noodles with vegetable oil 3) Modified whole milk with corn syrup solids 4) Lactose-hydrolyzed milk formula with corn syrup solids Intake of test material: 55 (first two days of treatment) and 110 kcal/kg bw/day for the following 4 days. -Intake of full-fat dried milk (modified) when fed alone: 17.4 g -Intake of full-fat dried milk (modified) when fed with wheat noodles: 8.7 g -No additional foods allowed.	Key results: 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. Authors' conclusion: "the noodle-milk diets employed during this study were safer than the milk diets for the dietary management of children with acute diarrhea."

Reference	Population	Intervention	Key Results
Fomon *et al*., 1981	Population: 81 normal healthy infants Age: 112-196 days	Duration: 12 weeks Test material: Pasteurized whole milk (n = 39) or heat treated milk (n=22) or Enfamil (n = 20) Intake of test material: 126-130 mL/kg bw/day at 112-139 days (~79% energy), 110-118 mL/kg bw/day at 140-167 days (~75% energy), 96-102 mL/kg bw/day at 168-195 days (~73% energy) -Weaning foods allowed, including milk	Key results: Incidence of blood in stool was greater among infants fed whole milk vs heat treated milk or formula from age 112 to 140 days; no difference thereafter. No significant differences observed in mean hemoglobin, hematocrit, serum iron, total iron-binding capacity, or transferrin saturation. *(Note: no iron supplementation was provided with whole milk)* Authors' conclusion: Pasteurized cow milk should not be administered prior to 140 days of age.
Hjelt *et al*., 1989	Population: 52 infants and children hospitalized with acute gastroenteritis after oral rehydration Age range: 6-46 months Mean age: 19 months	Duration: 7 days Test material: Rapid refeeding (lactose-limited whole milk as only fluid intake; n = 27) or gradual refeeding (stepwise intake with each step lasting 1+ days, first three steps excluding whole milk, 2nd step including "small amounts of cultured milk products," 3rd step including presumably typical amounts of cultured milk products, and 4th and last step including whole milk in "increasing amounts"; n = 25) In rapid refeeding (lactose-hydrolyzed) provided 47-59% of daily energy intake. No whole milk quantity provided for gradual refeeding. No limitations on additional foods & liquids in rapid refeeding	Key results: Both 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 compared to the gradual-refeeding group. Milk provided 47-59% of the daily energy intake of the rapid-refeeding group. Authors' conclusion: Whole milk was well accepted and no signs of cow's milk protein intolerance were observed. Additionally, the milk-based rapid-refeeding regimen can be employed "without the fear of negative effects on the outcome."
Isoulauri *et al*., 1986	Population: 65 infants and toddlers hospitalized for acute gastroenteritis Age range: 6-34 months	Duration: acute Test material: Whole milk and milk products (gruel, sour milk, yogurt, ice cream) (n = 38) or no milk (n = 27)	Key results: No difference observed between the groups in the clinical recovery from diarrhea; no prolonged diarrhea reported in any child; no new cases of clinical atopy were observed at 1-month follow-up; and no significant increases in the total or milk-specific IgE levels were reported. In addition, serum IgG and IgA antibodies to β-lactoglobulin and

Reference	Population	Intervention	Key Results
	Mean age: 14.7months	Milk-based products made up 30-90% total caloric intake; mean 50%, or approximately 400 kcal in first 18 h. All children received mixed diet:	α-casein were initially present in the majority of the children, but no appreciable changes in the antibodies were reported after gastroenteritis regardless of the type of diet. Authors' conclusion: Cow milk and milk products can be safely administered in acute gastroenteritis as parts of the mixed diet for children > 6 months of age
Larnkjær *et al*., 2009	Population: 83 healthy infants Mean age: 9.1±0.3 months, followed to age 12.1±0.3 months	Duration: 3 months Test material: Whole milk or infant formula, with or without fish oil. No recommendations on the amount of milk intake. Intake of test material: 300 ml/day, 30% of daily protein intake. Weaning foods allowed, including milk	Key results: Intake of whole milk significantly increased protein energy percentage and serum urea nitrogen; no effect on anthropometric measures of growth was observed; whole-milk intervention increased IGF-I in boys but not in girls; intake of fish oil had no effect on the outcomes. Authors' conclusion: "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."
Stekel *et al*., 1988	Population: 554 infants with birthweight >2500 g Age: 3-15 months (Measured at 3, 9, 15 months)	Duration: 12 months Test material: Whole milk with sucrose and corn flour supplemented with ferrous sulfate & ascorbic acid (n=276) or control milk without additives (n=278) Intake of test material: not reported Weaning foods allowed, including milk. Those breastfeeding were allowed to continue to do so.	Key results: 2.5% of infants in the group receiving whole milk + supplements had iron deficiency anemia compared with 25.7% of the control group. Authors' conclusion: "the acceptability of this milk was excellent."
Ziegler *et al*., 1990	Population: 52 healthy term infants	Duration: 12 weeks	Key results: No differences reported between groups in parental reports of regurgitation, vomiting, constipation, or other feeding-related behavior; stool

Reference	Population	Intervention	Key Results
	Age: 24 weeks	Test material: Whole cow's milk or infant formula (n=26/group) Intake of test material: not reported. Weaning foods allowed, including milk	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. No increase in stool hemoglobin among formula-fed infants and levels were 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, while the proportion of positive stools remained low (5.0%) with formula feeding. The proportion of occult-blood-positive stools among whole-milk-fed infants declined later, but remained significantly elevated for the entire trial. Authors' conclusion: "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."

Appendix D, Table 2. Clinical studies of infants consuming formula with dairy fat

Reference	Population	Intervention	Key Results
Breij *et al*., 2019	Parallel study 223 healthy infants ≤35 days Completers: 81 in control group, 87 in test group, 69 in breast fed group	Consumed from enrollment to age 17 weeks: Test: 48% dairy lipid; blend with plant oils; larger diameter lipid droplets with milk phospholipid coating; increased sn-2 palmitic acid content Control: plant oils formula	-No difference in gains of weight, length, or head circumference between test and control formula. -Lower daily mean formula intake in test group at weeks 13 and 17 compared with control formula; difference in weight adjusted formula intake not significantly different. -More frequent stool frequency in test group at week 13, increased diarrhea incidence at weeks 5, 8 and 13, and increased occurrence of regurgitation at weeks 5, 13 and 17; no effect on vomiting. -No difference AEs/SAEs. -No effect on plasma vitamin A or vitamin E. Author's conclusion: "supports adequate growth and is well tolerated and safe for use in infants."
De Souza *et al*., 2018; Leite *et al*., 2013	Crossover study 33 infants age 68 - 159 ± 3 days during each intervention; metabolic testing in 17 males	Consumed for 2 weeks: Test: 2.8% milk fat with plant oils with ARA and DHA Control: plant oils with ARA and DHA	-No effect on formula intake and adverse effects. -Increased stool frequency and percentage of formed stools with consumption of the formula containing milk fat and palm olein during the metabolic observation; no difference during tolerance period
Manios *et al*., 2020	Crossover study 16 healthy, formula-fed infants, age 9-14 weeks	Consumed for 2 weeks: Test: 50% milk fat; blend with vegetable fat Control: vegetable fat	-No difference in formula intake, weight or length measurements -No difference in total free fatty acids, though proportions of some individual fatty acids differed (excluding palmitic acid) -No difference in palmitic acid concentration in stool, but proportion of palmitic acid in stool relative to total free fatty acids was decreased compared to vegetable fat control -Decreased calcium concentration in stool compared to vegetable fat control -Decreased stool consistency and more reports of watery stools compared to vegetable fat control
Manios *et al*., 2020	Crossover study	Consumed for 2 weeks:	-No difference in formula intake, weight or length measurements

Reference	Population	Intervention	Key Results
	17 healthy, formula-fed infants, age 9-14 weeks	Test: 20% milk fat; blend with vegetable fat Control: vegetable fat	- No difference in total free fatty acids, though proportions of some individual fatty acids differed (excluding palmitic acid) - Decreased calcium concentration in stool compared to vegetable fat control -No difference in stool consistency
Schouten, 2013 [unpublished, as cited in GRN 898]	Single arm trial; open label 50 healthy term infants	Consumed for 6 weeks: 49% milk fat by weight in fat blend	-Based on data from a historical control group of Asian infants, no difference in the severity and occurrence of gastrointestinal symptoms was observed.

Adapted from GRN 898. Abbreviations: AE - adverse events; ARA - arachidonic acid; DHA - docosahexaenoic acid; RBC - red blood cells; SAE - serious adverse events

From: Mary Murphy
To: Morissette, Rachel
Subject: [EXTERNAL] RE: questions for GRN 1041
Date: Wednesday, April 13, 2022 2:21:40 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
2101743.000 - 5050_Responses to FDA Clarifying Questions on GRN 1041.pdf

---

Dear Rachel,

Please find attached our responses to your questions on GRN 1041. If you have further questions, please let us know.

Thank you,
Mary

Mary Murphy
Exponent
Direct +1-202-772-4953
Email mmurphy@exponent.com

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Friday, April 1, 2022 7:49 AM
To: Mary Murphy <mmurphy@exponent.com>
Subject: [EXTERNAL] questions for GRN 1041

Dear Ms. Murphy,

Please see attached our questions for GRN 001041. Let me know if you have questions.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist/Biologist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

QUESTION 1

We note that on Form 3667 you checked yes for boxes 7-9, indicating that there is data and information contained in the notice that you consider confidential or trade secret. Further, you provided us with a redacted notice indicating that the supplier information in Appendix A is exempt from disclosure. However, in Part 1 "Exemptions from Disclosure" of both the redacted and unredacted versions of the notice you provided you state the following:

> "Our view is that none of the data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the Freedom of Information Act (FOIA)."

Please clarify this discrepancy and provide a revised Part 1 of the notice indicating what data and information you view as exempt from disclosure under FOIA.

RESPONSE to Question 1

We apologize for the discrepancy. A revised Part 1 is provided in Attachment 1. Part 1 "Exemptions from Disclosure" has been updated as follows:

The supplier name on the ingredient information referenced in Appendix A is confidential commercial information exempt from disclosure under the Freedom of Information Act ("FOIA"). None of the remaining data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the FOIA. We therefore have provided a redacted version of the notice; the redacted version of the notice maintains the confidentiality of the ingredient supplier but does not otherwise obscure any information contained in the notice.

QUESTION 2

On page 9 of the notice, the intended use of dry whole milk is described as an ingredient in milk-based, non-exempt infant formula for healthy term infants. Please confirm whether "milk-based" refers to cow milk.

RESPONSE to Question 2

Yes, the reference to milk-based non-exempt infant formula for healthy term infants refers to formula based on cow milk.

QUESTION 3

On page 28 in Part 4 of the notice, Nara Organics states that the typical whey-to-casein protein ratio of bovine milk is 20:80. Please confirm that the whey-to-casein ratio of the notified dry whole milk ingredient has the same whey:casein ratio (20:80).

RESPONSE to Question 3

The dry whole milk ingredient is derived from typical bovine milk and therefore the whey-to-casein ratio of the ingredient can reasonably be assumed to be a ratio of approximately 20:80 based on standard reference data.[1] Analytical data also demonstrate that the whey:casein ratio is 20:80, as summarized below.

Analysis of whey:casein ratio in dry whole milk sample[a]

Protein Component	**g/100 g**	**% of total**	**whey:casein ratio[b]**
Whey[c]	5.60	19.9	20:80
Casein	22.53	80.1	
Total	28.13	-	

[a] Protein in dry whole milk sample was quantified using SDS slab gel electrophoresis according to the method of Laemmli (Laemmli UK. Nature 227:680-685, 1970) as described by Burgess-Cassler et al. (Clin. Chem. 35:2297-2304, 1989); the non-protein nitrogen (NPN) fraction was determined with method AOAC 999.21. Results represent analysis of one sample in duplicate on two gels for a total of four measurements.
[b] Rounded to the nearest integer.
[c] Non-protein nitrogen (NPN) removed.

[1] Miller GD, Jarvis JK, McBean LD. 2007. Editors in: *Handbook of Dairy Foods and Nutrition, Third Edition.* National Dairy Council, CRC Press: New York.

QUESTION 4

Table 6 on page 19 of the notice cites ISO method 160140 for detection of *Salmonella* spp. and *Listeria monocytogenes*. We note that the method should be ISO 16140, titled "Microbiology of the food chain." Please confirm the ISO method number. Further, the sampling specifications for *Salmonella* spp. are listed in Table 6 as 375 g. Please state whether Nara Organics analyzes multiple samples of product or one 375 g sample for determination of *Salmonella* spp. We recommend that *Salmonella* testing be performed on sample sizes no larger than 25 g to prevent the possibility of false negatives, unless the method used is validated for larger samples. If the analysis is performed on a sample size larger than 25 g, please discuss the method and whether it is validated.

RESPONSE to Question 4

We apologize for a typographical error in the ISO method. The correct number for the ISO method is 16140; an updated Table 6 with the corrected method citations is provided below. For *Salmonella* spp., a 375g sample unit of the dry whole milk was analyzed using Bio-Rad iQ Check *Salmonella*, a molecular detection method.[2] The Bio-Rad iQ Check *Salmonella* assay was validated using 375g samples for infant formula and ingredients used in infant formula. The validation study was performed as a comparison to reference method ISO 6579-1:2017 and certified by AFNOR using the NF validation protocol ISO 16140.[3] Results from the validation study demonstrate equivalence in performance of the ISO 6579-1:2017 method and the Bio-Rad iQ Check *Salmonella* test. For *Listeria monocytogenes*, the Bio-Rad iQ Check Listeria assay was used to analyze the dry whole milk samples; similarly, the method is validated by AFNOR (using the NF validation protocol ISO 16140) as equivalent to ISO 11290-1.[4]

REVISED Table 1. Specifications for Nara Organics dry whole milk intended for use in infant formula

Parameter	Specification	Method
Moisture	NMT 4.5%	AOAC 927.05
Milk fat	NLT 26 NMT 35%	AOAC 932.06
Protein	NLT 22% NMT 30%	AOAC 991.20
Scorched particles	NMT Disk B (15 mg)	ADPI
Titratable Acidity	NMT 0.15%	ISO 6092:1980
Insolubility Index	NMT 1.0 mL	ADPI
Ash	NMT 7%	AOAC 923.03

[2] Molecular detection methods are used to assess compliance with microbiological specifications in infant formula ingredients, e.g., the molecular detection method AOAC 2016.01 is used to monitor *Salmonella* spp. in dry whole milk as noted in GRN 980.
[3] https://nf-validation.afnor.org/en/wp-content/uploads/sites/2/2014/03/Synt-BRD-07-06-07-04_fr.pdf
[4] https://nf-validation.afnor.org/wp-content/uploads/2014/03/Synt-BRD-07-10-04-05-_fr.pdf

Parameter	Specification	Method
Peroxide Value	NMT 5 meq/kg fat	AOAC 965.33
Cholesterol	NMT 150 mg/100 g	AOAC 994.10
Vitamin A	NMT 1500 IU/100 g	AOAC 992.04, 992.06, 2001.13
Vitamin D3	NMT 10 IU/100 g	AOAC 2011.11
Iron	NMT 1 mg/100 g	AOAC 984.27, 985.01, 2011.14
Iodine	NMT 500 mcg/100 g	AOAC 2012.15
Selenium	NMT 30 mcg/100 g	AOAC 2011.19
Sodium	NMT 500 mg/100 g	AOAC 984.27, 985.01, 2011.14
Potassium	NMT 1600 mg/100 g	AOAC 984.27, 985.01, 2011.14
Chloride	NMT 1200 mg/100 g	AOAC 963.05, 971.27, 986.26
Microbiological		
Aerobic Plate Count	<10,000 cfu/g	ISO 4833:2003
Coliforms	<10 cfu/g	ISO 4832:2006
Yeast	<100 cfu/g	FDA BAM, Ch 18
Mold	<100 cfu/g	FDA BAM, Ch 18
Salmonella spp.	Negative / 375g	ISO (ANFOR) 16140 / 6579
Listeria monocytogenes	Negative / 25g	ISO (ANFOR) 16140 / 11290-1
Staphylococcus (Coagulase +)	<10 cfu/g	ISO 6888-1
Bacillus cereus	<100 cfu/g	ISO 7932
Enterobacteriaceae	<10 cfu/g	ISO 21528-2
Cronobacter spp.	Not detected / 10g	ISO 22964:2017-04
Heavy Metals		
Lead	NMT 50 mcg/kg	AOAC 2011.19, 993.14
Arsenic	NMT 100 mcg/kg	AOAC 2011.19, 993.14
Cadmium	NMT 50 mcg/kg	AOAC 2011.19, 993.14
Mercury	NMT 50 mcg/kg	AOAC 2011.19, 993.14

QUESTION 5

We note that in Table 7 on page 19 of the notice, the reported results for titratable acidity are between 10 and 11%; however, the specified limit is listed as ≤0.15%. Please address this discrepancy in the batch analysis results compared to the specified limit.

RESPONSE to Question 5

We apologize for this error; an updated Table 7 with the corrected values is provided below. The batch data demonstrate that the dry whole milk meets the established specification for titratable acidity.

REVISED Table 2. Analytical results of three non-consecutive lots compared to Nara Organics dry whole milk specifications

Parameter	Nara Organics Specification	Analyzed Lots		
		2127210601	**2127210711**	**2127192531**
Moisture	NMT 4.5%	2.8	2.4	2.8
Milk fat	26 – 35%	30.2	29.7	30.3
Protein	22 – 30%	25.6	25.8	27.1
Scorched Particles	NMT Disk B (15 mg)	7.5	7.5	7.5
Titratable Acidity	NMT 0.15%	0.11	0.11	0.12
Insolubility Index	NMT 1.0 mL	0.1	0.1	0.175
Ash	NMT 7%	5.3	5.4	5.1
Peroxide Value	NMT 5 meq/kg fat	1.4	1.3	1.4
Cholesterol	NMT 150 mg/100 g	101	108	107
Vitamin A	NMT 1500 IU/100 g	662	707	609
Vitamin D3	NMT 10 IU/100 g	<4.00	<4.00	<4.00
Iron	NMT 1 mg/100 g	<0.248	<0.248	<0.243
Iodine	NMT 500 mcg/100 g	244	160	155
Selenium	NMT 30 mcg/100 g	15.7	16.4	17.3
Sodium	NMT 500 mg/100 g	265	279	278
Potassium	NMT 1600 mg/100 g	1130	1110	1160
Chloride	NMT 1200 mg/100 g	705	731	750
Microbiological				
Aerobic Plate Count	<10,000 cfu/g	210	150	130
Coliforms	<10 cfu/g	<10	<10	<10
Yeast	<100 cfu/g	<10	10	<10
Mold	<100 cfu/g	20	<10	<10
Salmonella spp.	Negative / 375g	Negative	Negative	Negative
Listeria monocytogenes	Negative / 25g	Negative	Negative	Negative
Staphylococcus (Coagulase +)	<10 cfu/g	<10	<10	<10

Parameter	Nara Organics Specification	Analyzed Lots		
		2127210601	**2127210711**	**2127192531**
Bacillus cereus	<100 cfu/g	<100	<100	<100
Enterobacteriaceae	<10 cfu/g	<10	<10	<10
Cronobacter spp.	Not detected / 10g	Not detected	Not detected	Not Detected
Heavy Metals				
Lead	NMT 50 mcg/kg	<5.00	<5.00	<5.00
Arsenic	NMT 100 mcg/kg	<10.0	<10.0	<10.0
Cadmium	NMT 50 mcg/kg	<5.00	<5.00	<5.00
Mercury	NMT 50 mcg/kg	<5.00	<5.00	<5.00

Abbreviations: ADPI - American Dairy Products Institute; AOAC - Association of Official Analytical Collaboration; ISO - International Organization for Standardization; NMT - not more than.

Attachment 1: Revised Section 1

Part 1: Signed Statements and Certification

Nara Organics, Inc. submits to the U.S. Food and Drug Administration (FDA) this generally recognized as safe (GRAS) notice in accordance with 21 CFR part 170, subpart E.

Name and Address of Notifier

Nara Organics, Inc.
335 Madison Avenue, 4th Floor
New York, NY 10017

Notifier Contact:
Juan M Gonzalez, Ph.D.
Head of Research & Development
Nara Organics
335 Madison Avenue
4th Floor
New York, NY 10017
juan@naraorganics.com

with a copy to:
Jung Ma
Chief of Staff
Nara Organics
335 Madison Avenue
4th Floor
New York, NY 10017
jung@naraorganics.com

Agent Contact:
Mary M. Murphy, MS, RD
Exponent, Inc.
1150 Connecticut Avenue, NW
Washington, DC 20036
mmurphy@exponent.com

Name of GRAS Substance

The substance that is the subject of this GRAS notice is dry whole milk.

Intended Conditions of Use

The intended use of dry whole milk is as an ingredient in Nara Organics milk-based, non-exempt infant formula for healthy term infants at a maximum level of 22 g per 100 g infant formula powder.

Basis for Conclusion of GRAS Status

Nara Organics' conclusion of GRAS status for the intended use of dry whole milk in non-exempt infant formula for healthy term infants is based on scientific procedures in accordance with 21 CFR §170.30(a) and (b).

Pre-Market Approval Exclusion Claim

The intended use of dry whole milk in non-exempt infant formula is not subject to the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Nara Organics has concluded that such use is GRAS through scientific procedures.

Availability of Information

The data and information that serve as the basis for this GRAS conclusion will be sent to the FDA upon request, or are available for the FDA's review and copying during customary business hours at the office of Exponent, Inc., located at 1150 Connecticut Ave, NW, Washington, DC 20036.

Exemptions from Disclosure

The supplier name on the ingredient information referenced in Appendix A is confidential commercial information exempt from disclosure under the Freedom of Information Act ("FOIA"). None of the remaining data and information in Parts 2 through 7 of the GRAS notice are exempt from disclosure under the FOIA. We therefore have provided a redacted version of the notice; the redacted version of the notice maintains the confidentiality of the ingredient supplier but does not otherwise obscure any information contained in the notice.

Certification Statement

On behalf of Nara Organics, I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, 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.

Name: Juan M. Gonzalez, Ph.D.

April 12, 2022

Date: