GRN 1172

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February 22, 2024

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

Subject: GRAS Notice for the Use of Liquid Milk as an Ingredient in Non-Exempt Infant Formula

Dear Dr. Carlson:

In accordance with 21 CFR part 170, subpart E, Synlait Milk Limited hereby provides a notice of a claim that the food ingredient described in this submission is excluded from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because the notifier has concluded such use to be generally recognized as safe (GRAS), based on scientific procedures.

The materials in this submission include Form 3667 and one complete electronic copy of the GRAS notice. If you have any questions or require additional information, please do not hesitate to contact me at 202-772-4953 or mmurphy@exponent.com.

Sincerely,

Mary M. Murphy, MS, RD
Principal Scientist

Letter of Authorization

22 February 2024

Jessica Bernhardt
Electronic Submissions Gateway
U.S. Food and Drug Administration
3WFN, Room 7C34
12225 Wilkins Avenue
Rockville, MD 20852

Re: Authorization Letter

To whom it may concern:

Pursuant to Section 11.100 of Title 21 of the Code of Federal Regulations, please accept this Authorization Letter. This letter is to certify that Synlait Milk Limited authorizes Exponent, Inc. to submit in the Electronic Submissions Gateway on behalf of Synlait Milk Limited.

Sincerely yours,

Caroline Gain

Head of Global Regulatory Affairs

Generally Recognized As Safe Conclusion for the Use of Liquid Milk as an Ingredient in Non-Exempt Infant Formula

PREPARED FOR:

Synlait Milk Limited
1028 Heslerton Road
Rakaia 7783
New Zealand

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:

Exponent, Inc.
1150 Connecticut Avenue, NW
Washington, DC 20036

February 22, 2024

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List of Acronyms

ºC	degrees Celsius
µg	microgram
µmol	micromole
AMF	anhydrous milk fat
AOAC	Association of Official Analytical Collaboration
Bq	becquerel
bw	body weight
CFR	Code of Federal Regulations
cfu	colony forming unit
cGMP	current good manufacturing practices
CLA	conjugated linoleic acid
FDA	U.S. Food and Drug Administration
FDC	FoodData Central
g	gram
GRAS	generally recognized as safe
GRN	GRAS notice
h	hour
HPLC	high-performance liquid chromatography
ISO	International Organization for Standardization
IU	International Unit
kcal	kilocalorie
kg	kilogram
L	liter
m	meter
MFGM	milk fat globule membrane
mg	milligram
mL	milliliter
m/m	mass for mass
MPN	most probable number
MS	milk solids
NCCP	National Chemical Contaminants Programme
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
PDCAAS	protein digestibility corrected amino acid score

PER	protein efficiency ratio
pg	picogram
pH	potential hydrogen
PMO	Pasteurized Milk Ordinance
ppm	parts per million
RMP	Risk Management Programme
SML	Synlait Milk Limited
U.S.	United States
USDA	United States Department of Agriculture
w/w	weight for weight
wt	weight
WWEIA	What We Eat in America

Part 1. Signed Statements and Certification

1.1. Introduction

Synlait Milk Limited (SML) 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.

1.2. Name and Address of Notifier

Synlait Milk Limited
1028 Heslerton Road
Rakaia 7783
New Zealand

1.3. Name of GRAS Substance

The substance that is the subject of this GRAS notice is liquid milk, composed of whole and nonfat milk in a combined form with lactose and water in approximate 4:1:1:4 proportions by weight, and pasteurized. The substance is referenced as liquid milk herein.

1.4. Intended Conditions of Use

The intended use of liquid milk is as an ingredient in milk-based, non-exempt infant formula for healthy term infants at a maximum level of 25 g liquid milk solids per 100 g infant formula powder.

1.5. Basis for Conclusion of GRAS Status

SML's conclusion of GRAS status for the intended use of liquid milk as an ingredient in milk-based, non-exempt infant formula for healthy term infants is based on scientific procedures in accordance with 21 CFR §170.30(a) and (b).

1.6. Pre-Market Approval Exclusion Claim

The intended use of liquid milk as an ingredient in milk-based, non-exempt infant formula for healthy term infants is not subject to the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because SML has concluded that such use is GRAS through scientific procedures.

1.7. 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 Mary Murphy, Principal Scientist, Exponent, Inc., located at 1150 Connecticut Ave, NW, Washington, DC 20036.

1.8. 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).

1.9. Certification Statement

On behalf of Synlait Milk Limited, 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 liquid milk.

22 February 2024

Caroline Gain
Synlait Milk Limited

Date

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

2.1. Common or Usual Name

The substance that is the subject of this GRAS notice is liquid milk, composed of whole and nonfat milk in a combined form with lactose and water in approximate 4:1:1:4 proportions by weight, and pasteurized.

2.2. Identity

Liquid milk represents a combination of whole milk, nonfat milk, an aqueous lactose solution (18% lactose by weight), and water. The components are combined in specified proportions and pasteurized. The resulting liquid milk provides a standard solids and macronutrient composition for use of liquid milk in the production of infant formula. The fluid milk components in liquid milk, namely fluid whole milk and fluid nonfat milk, are sourced from dairy cows in New Zealand.

2.3. Composition

2.3.1. Macronutrients

The macronutrient composition of liquid milk reflects the macronutrient composition of whole milk in combination with nonfat milk, the aqueous lactose solution (18% lactose by weight), and water. The typical macronutrient composition of liquid milk is summarized in Table 1; compositional data for whole milk and nonfat milk as reflected in data from the USDA also are presented for comparison. On an as is basis, liquid milk has a lower solids content relative to fluid whole milk or fluid nonfat milk. On a dry weight basis, the concentration of carbohydrate (lactose) in liquid milk is similar to the concentration of carbohydrate in nonfat milk; the remaining solids in liquid milk are present at similar concentrations of protein and fat, and the balance present as ash.

Table 1. Typical macronutrient composition of liquid milk relative to whole milk and nonfat milk

Component	Unit	Liquid Milk Average of 4 Batches[a]	USDA Whole Milk[b]	USDA Nonfat Milk[b]
Total solids	%, as is	7.5	11.9	9.2

Component	Unit	Liquid Milk Average of 4 Batches[a]	USDA Whole Milk[b]	USDA Nonfat Milk[b]
Protein	%, as is	1.6	3.3	3.4
Fat	%, as is	1.5	3.2	0.1
Ash	%, as is	0.3	0.8	0.8
Carbohydrate	%, as is	4.0	4.6	4.9
Protein	%, dry wt	22.0	27.5	37.3
Fat	%, dry wt	20.6	26.9	0.9
Ash	%, dry wt	4.2	6.7	8.4
Carbohydrate	%, dry wt	53.3	38.9	53.5

[a] Values represent average of samples from 4 non-consecutive batches of liquid milk; values do not add up to total solids or 100% dry weight due to rounding. Specifications for these components are identified in Table 5.
[b] Dry weight composition of USDA whole milk (FDC ID 746782; USDA, 2019a) and USDA nonfat milk (FDC ID 746776; USDA, 2019b) calculated from data for fluid milk assuming 11.9% and 9.2% dry matter, respectively.

There is inherent variability in the nutritional profile of agricultural products such as milk due to factors including but not limited to breed, environment and management, animal health and physiology, and nutrition (Linn, 1988). The controlled production process of the liquid milk results in an ingredient with a standard solids and macronutrient composition. Average concentrations of fatty acids (dry weight basis), amino acids (dry weight basis and per 100 g protein), and micronutrient constituents in liquid milk (dry weight basis) are summarized in Table 2, Table 3, and Table 4, respectively, based on analysis of representative samples of liquid milk. These values in liquid milk thus represent typical values, though some variability is not unexpected. For comparison, each table presents the average concentration of the nutrients in fluid whole milk as reported by USDA, calculated on a dry weight basis. Consistent with the macronutrient comparisons shown in Table 1, these data demonstrate that on a dry weight basis, the concentrations of individual fatty acids, amino acids, and micronutrients in liquid milk are generally lower than concentrations of the corresponding components in whole milk, though relative concentrations of the components in liquid milk and whole milk, and relative concentrations of amino acids per 100 g protein, are similar.

2.3.2. Fatty Acids

Table 2. Typical fatty acid composition of liquid milk, g per 100 g liquid milk solids

Component	Unit	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]
Capric, C10:0	g/100 g, dry wt	0.64 [0.60-0.71]	0.71
Lauric, C12:0	g/100 g, dry wt	0.86 [0.77-0.94]	0.82
Myristic, C14:0	g/100 g, dry wt	2.38 [2.14-2.67]	2.60

Component	Unit	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]
Palmitic, C16:0	g/100 g, dry wt	5.90 [5.35-6.40]	7.20
Palmitoleic, C16:1	g/100 g, dry wt	0.28 [0.26-0.32]	0.33
Stearic, C18:0	g/100 g, dry wt	1.81 [1.74-1.90]	2.60
Oleic, C18:1n-9	g/100 g, dry wt	3.22 [3.07-3.35]	5.10
Linoleic, C18:2n-6	g/100 g, dry wt	0.17 [0.15-0.19]	0.71
Alpha linolenic, C18:3n-3	g/100 g, dry wt	0.15 [0.13-0.17]	0.10
Saturated fat	g/100 g, dry wt	13.7 [13.4-14.7]	15.6
Monounsaturated fat	g/100 g, dry wt	4.0 [4.0-4.1]	5.80
Polyunsaturated fat	g/100 g, dry wt	1.3 [1.3-1.4]	0.91
Trans fat (total)	g/100 g, dry wt	1.3 [1.3-1.4]	0.94

[a] Values represent average of samples from 4 non-consecutive batches of liquid milk calculated on a dry weight basis; minimum and maximum values in brackets indicate range for these samples.
[b] Dry weight composition of USDA whole milk (FDC ID 746782; USDA 2019a) calculated from data for fluid whole milk assuming 11.9% dry matter (see Table 1).

2.3.3. Amino Acids

Table 3. Typical amino acid composition of liquid milk, g per 100 g liquid milk solids and g per100 g protein

Component	g/100 g, dry wt		g/100 g protein	
	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]
Alanine	0.71 [0.70-0.72]	0.92	3.2 [3.1-3.3]	3.4
Arginine	0.73 [0.71-0.75]	1.07	3.3 [3.3-3.4]	3.9
Aspartic acid (asparagine + aspartic acid)	1.61 [1.59-1.63]	2.34	7.3 [7.3-7.4]	8.5
Cystine (cysteine + cystine)	0.15 [0.13-0.17]	0.32	0.7 [0.6-0.8]	1.2
Glutamic acid (glutamine + glutamic acid)	4.54 [4.49-4.65]	6.62	20.6 [20.4-21.0]	24.1
Glycine	0.43 [0.38-0.49]	0.58	2.0 [1.8-2.2]	2.1
Histidine	0.57 [0.52-0.61]	0.82	2.6 [2.4-2.7]	3.0
Isoleucine	1.16 [1.13-1.19]	1.45	5.3 [5.2-5.4]	5.3
Leucine	2.06 [2.03-2.09]	2.80	9.4 [9.3-9.4]	10.2
Lysine	1.74 [1.71-1.76]	2.50	7.9 [7.8-8.0]	9.1
Methionine	0.56 [0.55-0.58]	0.76	2.6 [2.5-2.6]	2.8
Phenylalanine	1.03 [1.00-1.05]	1.35	4.7 [4.6-4.8]	4.9
Proline	2.02 [1.91-2.11]	2.80	9.2 [8.8-9.5]	10.2
Serine	1.32 [1.29-1.37]	1.58	6.0 [5.9-6.2]	5.7

Component	g/100 g, dry wt		g/100 g protein	
	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]
Threonine	0.97 [0.96-0.99]	1.29	4.4 [4.4-4.5]	4.7
Tryptophan	0.28 [0.27-0.30]	0.36	1.3 [1.2-1.3]	1.3
Tyrosine	1.11 [1.08-1.13]	1.36	5.0 [5.0-5.1]	5.0
Valine	1.37 [1.28-1.44]	1.74	6.2 [5.9-6.5]	6.3

[a] Values represent average of samples from 4 non-consecutive batches of liquid milk calculated on a dry weight basis; minimum and maximum values in brackets indicate range for these samples.
[b] Dry weight composition of USDA whole milk (FDC ID 746782; USDA 2019a) calculated from data for fluid whole milk assuming 11.9% dry matter (see Table 1).

2.3.4. Micronutrients

Table 4. Typical select micronutrient composition of liquid milk, per 100 g liquid milk solids

Component	Unit	Liquid Milk Average and Range of 4 Batches[a]	USDA Whole Milk[b]
Vitamin A	IU/100 g, dry wt	690 [588-846]	870[c]
Vitamin D_3	IU/100 g, dry wt	<270[d]	34
Iron	mg/100 g, dry wt	<0.34[d]	0
Iodine	µg/100 g, dry wt	40 [23-57]	308
Selenium	µg/100 g, dry wt	7 [6-11]	16
Sodium	mg/100 g, dry wt	191 [163-228]	319
Potassium	mg/100 g, dry wt	841 [643-976]	1261
Chloride	mg/100 g, dry wt	510 [495-521]	-
Calcium	mg/100 g, dry wt	741 [678-802]	1034
Magnesium	mg/100 g, dry wt	65 [61-71]	100
Phosphorus	mg/100 g, dry wt	553 [522-628]	849
Zinc	mg/100 g, dry wt	2.3 [2-2.5]	3.5
Vitamin B2	mg/100 g, dry wt	1.68 [1.51-1.82]	1.16
Vitamin B12	µg/100 g, dry wt	2.4 [2.2-3.1]	4.54

[a] Values represent average of samples from 4 non-consecutive batches of liquid milk calculated on a dry weight basis; minimum and maximum values in brackets indicate range for these samples.
[b] Dry weight composition of USDA whole milk (FDC ID 746782; USDA 2019a) calculated from data for fluid whole milk assuming 11.9% dry matter (see Table 1). Value for vitamin D was calculated from USDA whole milk without added vitamin A and vitamin D data (FDC ID 172217; USDA 2019c).
[c] Calculated from retinol concentration of 261 µg Retinol Activity Equivalents in USDA whole milk (FDC ID 746782; USDA 2019a) on a dry weight basis and assuming 1 IU retinol = 0.3 µg Retinol Activity Equivalents.
[d] Calculated from level of detection (LOD) for analysis in liquid milk (as is) and assuming the minimum concentration of solids (7.3 g per 100 g liquid milk). LOD per 100 g liquid milk (as is) is 20 IU [0.50 µg] for vitamin D_3 and 0.025 mg for iron; calculated LOD per 100 g liquid milk solids is 270 IU [6.8 µg] vitamin D_3, and 0.34 mg iron.

2.4. Production Process

2.4.1. Materials

The starting materials used to produce liquid milk are raw milk, lactose, and water. The incoming raw milk used to produce the ingredient meets New Zealand Regulations (Animal Products Act 1999[1] and Animal Products Regulations 2021[2]) which ensure the milk is suitable for the intended use. Monitoring data on the incoming milk, including assessment of mycotoxins, environmental contaminants, veterinary drug residues, and pesticide residues, demonstrate compliance of the incoming raw milk with requirements of the 2019 Pasteurized Milk Ordinance (PMO) in the U.S. Monitoring data on the incoming raw milk are summarized in Appendix A. The lactose used to make the liquid milk is food-grade and meets the regulatory definition for this ingredient (21 CFR 168.122); a representative certificate of analysis is provided in Appendix A.

2.4.2. Process

The liquid milk is manufactured under conditions of current good manufacturing practices (cGMP) at a dairy processing facility (U.S. FDA Registration 15930127872),which operates under a Risk Management Programme (RMP) registered with the Ministry for Primary Industries (MPI), the regulator of dairy processing and export in New Zealand. Under the RMP, facilities and processing are independently audited and verified by a government approved third-party agency, on a maximum 6-weekly rotation. Additionally, the manufacture of liquid milk is subject to the requirements of the Animal Products Notice: Manufacture of Dairy Based Infant Formula Products and Formulated Supplementary Foods for Young Children (MPI, 23 June 2022)[3]. The SML manufacturing sites also hold FSSC22000 accreditation for the manufacture of infant formula products.

The production process is outlined in Figure 1. The manufacturing process employs standard dairy processing steps to produce fluid whole milk and fluid nonfat milk from the incoming raw milk. The fluid raw whole milk, fluid raw nonfat milk, lactose (as 18% aqueous solution), and water are combined in an automated in-line mixer to produce liquid milk. No processing aids are added during production of the liquid milk. The liquid milk is subjected to heat treatment (75.5ºC for 15.3 seconds at a flow rate of 73.0 m^3/h), which is consistent with pasteurization under conditions equivalent with the applicable provisions of the PMO. The liquid milk is an integral

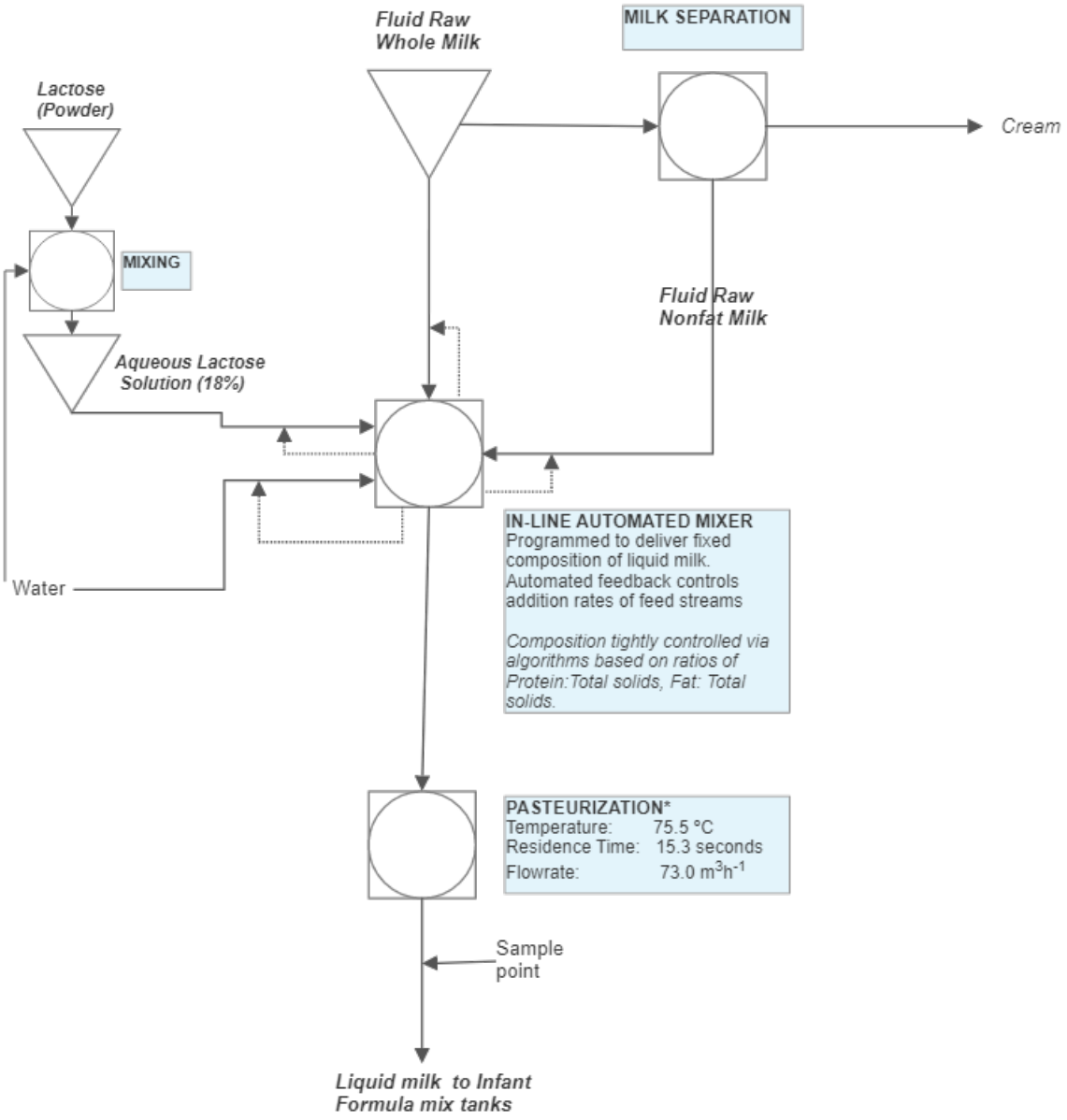
[1] https://www.legislation.govt.nz/act/public/1999/0093/latest/DLM33502.html

[2] https://www.legislation.govt.nz/regulation/public/2021/0400/latest/LMS520972.html

[3] https://www.mpi.govt.nz/dmsdocument/17647-Animal-Products-Notice-Manufacture-of-Dairy-Based-Infant-Formula-Products-and-Formulated-Supplementary-Foods-for-Young-Children

part of a continuous process for manufacture of infant formula powder. Immediately following the formation of the liquid milk, the liquid milk is delivered into mixing silos where other ingredients are added simultaneously, and the resulting formulation is subsequently dried to produce the final infant formula base powder.

Figure 1. Flow diagram of the production process of liquid milk



* Meets pasteurization conditions for milk product with lactose of 75 °C for 15 seconds as per PMO 2019 definition RR. PASTEURIZATION

2.5. Specifications

2.5.1. Product Specifications

Product specifications for the liquid 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. Liquid milk specifications (Table 5) include parameters for total solids, protein, fat, carbohydrate, ash, and select nutrients. Product specifications also include limits for heavy metals and potential microbiological contaminants. All methods of analysis are validated for the intended use.

Table 5. Specifications for liquid milk intended for use in infant formula

Parameter	Unit	Specification	Method
Total solids	%, as is	7.3-8.2	ISO 6731/IMF 21:2010
Protein	%, dry wt	21.3-23.3	ISO 8968-1/IDF 20-1:2014
Fat	%, dry wt	19.6-21.8	ISO 1211/IDF1: 2010
Ash	%, dry wt	2.4-5.1	BS 1741:1988 (modified)
Carbohydrate	%, dry wt	48.8-58.2	Calculation by difference
Cholesterol	mg/100 g, dry wt	<150	AOAC 933.08, 970.50, 970.51
Vitamin A	IU/100 g, dry wt	333-1200	AOAC 2012.10
Vitamin D_3	IU/100 g, dry wt	<270[a]	COST 91 (1986), J.M.A. 1 (1985)
Iron	mg/100g, dry wt	<0.34[a]	AOAC 2011.14 (ICP-OES)
Iodine	µg/100g, dry wt	<190	TMAH Digestion, ICP-MS
Selenium	µg/100g, dry wt	1-35	AOAC 2015.06 (TMAH Digestion (ICP-MS))
Sodium	mg/100g, dry wt	60-380	AOAC 2011.14 (ICP-OES)
Potassium	mg/100g, dry wt	360-1050	AOAC 2011.14 (ICP-OES)
Chloride	mg/100g, dry wt	220-860	AOAC 986.26
Microbiological			
Aerobic plate count	cfu/mL, as is	<1000	ISO 16140-2:2016
Coliforms	cfu/mL, as is	<50	AOAC 2018.13 (modified) (Rapid)
Escherichia coli	cfu/mL, as is	<1	AOAC 2018.13 (modified) (Rapid)
Salmonella	/25g, as is	Not Detected	ISO 6578-1:2017
Listeria monocytogenes	/25g, as is	Not Detected	ISO 11290-1:2017
Coagulase positive *Staphylococcus aureus*	/g, as is	0 MPN	ISO 6888-3:2003
Cronobacter species	/100g, as is	Not Detected	ISO 22964:2017
Bacillus cereus	cfu/mL, as is	<10	ISO 7932:2004
Heavy Metals			
Lead	mg/kg, as is	<0.005	AOAC 2015.06 (ICP-MS)
Cadmium	mg/kg, as is	<0.002	AOAC 2015.06 (ICP-MS)

Parameter	Unit	Specification	Method
Arsenic	mg/kg, as is	<0.003	AOAC 2015.06 (ICP-MS)
Mercury	mg/kg, as is	<0.005	AOAC 2015.06 (ICP-MS)

[a] Calculated from LOD for analysis in liquid milk (as is) and assuming the minimum concentration of solids (7.3 g per 100 g liquid milk). LOD per 100 g liquid milk (as is) is 20 IU [0.50 µg] for vitamin D_3 and 0.025 mg for iron; calculated LOD per 100 g liquid milk solids is 270 IU [6.8 µg] vitamin D_3, and 0.34 mg iron .

2.5.2. Batch Data

Analytical data from 4 non-consecutive batches as shown in Table 6 demonstrate the liquid milk ingredient complies with the stated specifications, indicating a production process that is in control and allows for consistent manufacturing of liquid milk.

Table 6. Analytical results of 4 non-consecutive batches of the liquid milk

Parameter	Unit	Specification	Batch #1487322	Batch #1556448	Batch #1627984	Batch #1628829
Total solids	%, as is	7.3-8.2	7.5	7.5	7.5	7.4
Protein	%, dry wt	21.3-23.3	22.0	21.8	22.1	22.1
Fat	%, dry wt	19.6-21.8	20.6	19.7	21.6	20.5
Ash	%, dry wt	2.4-5.1	3.3	4.7	4.4	4.3
Carbohydrate	%, dry wt	48.8-58.2	53.5	53.5	53.3	52.8
Cholesterol	mg/100 g, dry wt	<150	84	63	68	68
Vitamin A	IU /100g, dry wt	333-1200	846	659	588	670
Vitamin D_3	IU/100g, dry wt	<270[a]	<270	<270	<270	<270
Iron	mg/100g, dry wt	<0.34[a]	<0.34	<0.34	<0.34	<0.34
Iodine	µg/100g, dry wt	<190	23	57	36	43
Selenium	µg/100g, dry wt	1-35	7	11	6	6
Sodium	mg/100g, dry wt	60-380	228	201	173	163
Potassium	mg/100g, dry wt	360-1050	643	976	893	854
Chloride	mg/100g, dry wt	220-860	495	521	507	515
Microbiological						
Aerobic plate count	cfu/mL, as is	<1000	<100	<100	<100	<100
Coliforms	cfu/mL, as is	<50	<1	<1	<1	<1
Escherichia coli	cfu/mL, as is	<1	<1	<1	<1	<1
Salmonella	/25g, as is	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
Listeria monocytogenes	/25g, as is	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
Coagulase positive *Staphylococcus aureus*	/g, as is	0 MPN	0 MPN	0 MPN	0 MPN	0 MPN
Cronobacter species	/100g, as is	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected
Bacillus cereus	cfu/mL, as is	<10	<10	<10	<10	<10
Heavy Metals						
Lead	mg/kg, as is	<0.005	<0.005	<0.005	<0.005	<0.005
Cadmium	mg/kg, as is	<0.002	<0.002	<0.002	<0.002	<0.002
Arsenic	mg/kg, as is	<0.003	<0.003	<0.003	<0.003	<0.003

Parameter	Unit	Specification	Batch #1487322	Batch #1556448	Batch #1627984	Batch #1628829
Mercury	mg/kg, as is	<0.005	<0.005	<0.005	<0.005	<0.005

[a] Calculated from LOD for analysis in liquid milk (as is) and assuming the minimum concentration of solids (7.3 g per 100 g liquid milk). LOD per 100 g liquid milk (as is) is 20 IU [0.50 µg] for vitamin D_3 and 0.025 mg for iron; calculated LOD per 100 g liquid milk solids is 270 IU [6.8 µg] vitamin D_3, and 0.34 mg iron.

2.5.3. Monitoring of Potential Contaminants

As previously noted, SML routinely monitors incoming milk used to produce liquid milk for potential environmental contaminants to ensure hygienic control. Monitoring of the milk includes screening for veterinary drug residues, pesticides, and ionizing radiation (Appendix A). This monitoring demonstrates consistency with the PMO (21 CFR §1240.61), and applicable regulations or Compliance Policy Guides prescribing maximum limits and/or action levels for environmental contaminants, animal drugs, and pesticides in milk. Additionally, New Zealand actively monitors potential chemical contaminants in the dairy supply through the NCCP.

2.6. Stability

The liquid milk that is the subject of this notice is produced as an initial step that is part of a continuous process for manufacture of infant formula powder. Immediately following the formation of the liquid milk, the liquid milk is delivered into mixing silos where other ingredients are added simultaneously. The mixture is subsequently dried to produce the final infant formula powder. The liquid milk therefore is used immediately after formation; it is not stored and it is not subjected to stability testing.

2.7. Physical or Technical Effect

The liquid milk that is the subject of this notice is intended for use as an ingredient in milk-based, non-exempt infant formula for healthy term infants. The liquid milk ingredient will provide a source of macronutrients (i.e., protein, fat, and carbohydrate) in a nutritionally balanced infant formula.

Part 3. Dietary Exposure

3.1. Proposed Use and Level

The liquid 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, providing a source of macronutrients (i.e., protein, fat, and carbohydrate) in a nutritionally balanced infant formula. The maximum intended use of the liquid milk in infant formula is 25 g liquid milk solids per 100 g infant formula powder.

To estimate intake of liquid milk solids, it was assumed that approximately 20 g of a milk-based infant formula powder provides 100 kcal with a typical caloric density of 67 kcal per 100 mL, as prepared. The maximum intended use of liquid milk, 25 g liquid milk solids per 100 g infant formula powder, therefore corresponds approximately to 5.0 g liquid milk solids per 100 kcal infant formula powder and 3.4 g liquid milk solids per 100 mL reconstituted infant formula.

The liquid milk solids are predominantly whole milk solids (approximately 64% by weight), lactose (approximately 24% by weight), and nonfat milk solids (approximately 12% by weight). Other sources of whey proteins will be added to the infant formula to target a whey:casein ratio of 60:40 in the infant formula powder. Vegetable oils, nonfat milk solids, lactose, and vitamins and minerals will be added to the formulation to ensure the infant formula powder is nutritionally complete for infants and compliant with 21 CFR §107.100.

3.2. Estimated Daily Intake

3.2.1. Population and Representative Infant Formula

Intake of infant formula was estimated using dietary recall data collected in the What We Eat in America (WWEIA) dietary recall component of the National Health and Nutrition Examination Survey (NHANES). The WWEIA/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 in the first year of life.

Estimates of liquid milk solids intake from the intended use of liquid milk were developed from food consumption records collected in the WWEIA/NHANES (CDC, 2023). Data for this analysis represent the combined cycles from 2011-2012 to 2017-2018 (2011-2018). 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. Throughout these NHANES cycles, infant age at the time of the dietary recall component was recorded. The more recent NHANES data files, corresponding to the time period from 2017 to March 2020 (pre-Pandemic) provide age detail only at the time of the initial NHANES interview and do not provide details on infant age at the time of the exam and dietary recall. Given the absence of information on infant age at the time of the dietary recall, the 2017-March 2020 data were not used to estimate infant formula intake. Rather, infant formula intake was estimated with the WWEIA/NHANES 2011-2018 data. 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 survey data files processed by USDA provide the estimated energy intake for each item reported consumed in the dietary recall. In this analysis, all infant formulas providing 62 kcal to 67 kcal per 100 g food code (representing reconstituted infant formula) were assumed to reflect consumption of milk-based, non-exempt infant formula for healthy term infants, as this energy density generally aligns with the recommended energy density of infant formula of 63 kcal to 71 kcal per 100 mL (Raiten *et al*., 1998), and the Codex Standard of 60 to 70 kcal per 100 mL (CAC, 2020). The remaining infant formulas reported consumed in NHANES provided ≥71 kcal per 100 g or <60 kcal per 100 g and thus have an energy density inconsistent with typical formulas for healthy term infants. A list of food codes used in the analysis to develop representative estimates of energy intake from infant formula and in turn liquid milk solids is provided in Appendix B.

3.2.2. Analysis

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 liquid milk solids from the intended use in infant formula was calculated assuming 5.0 g liquid milk solids per 100 kcal infant formula powder and 3.4 g liquid milk solids per 100 mL reconstituted infant formula.

Estimated 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 liquid milk solids from infant formula powder/day and g liquid milk solids as an ingredient in infant formula powder/day) and intake per kilogram body weight per day (kcal liquid milk solids from infant formula/kg bw/day and g liquid milk solids 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 include infants consuming infant formula as a sole source of nutrition or in combination with human milk and/or table foods. Infants not consuming a selected infant formula presumably consumed human milk and/or table foods, or an infant formula excluded from this assessment. The estimates of infant formula intake were derived using the Foods Analysis and Residues Evaluation Program (FARE® version 15.11) 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.

3.2.3. Results

Estimated daily intakes of energy from infant formula based on WWEIA/NHANES 2011-2018 are summarized in Table 7 below. The estimated daily energy intake from infant formula was highest among infants 3-5 months of age with mean and 90th percentile intakes of 558 and 860 kcal/day, respectively. On a body weight basis, the highest daily energy intake from infant formula was among infants 0-2 months of age, with mean and 90th percentile intakes of 96 and 146 kcal/kg bw/day, respectively. Relative to intake in the first six months of life, intake of infant formula in the second six months of life was lower expressed as both kcal/day and kcal/kg bw/day.

Table 7. Per user estimated daily intake of energy from infant formula, What We Eat In America/National Health and Nutrition Examination Survey (WWEIA/NHANES) 2011-2018

Age, months	Total Sample[a]	Users[b]		kcal/day		kcal /kg bw/day	
		Number	Weighted Percent	Mean	90th Percentile	Mean	90th Percentile
0-2	250	161	60.4	490	765	96	146
3-5	346	252	65.7	558	860	81	122
6-8	295	232	75.5	502	733	61	97
9-11	303	231	76.6	452	709	48	76

[a] Total sample represents unweighted number of infants with 2 days of recall data in the sample.
[b] Users number represents unweighted number of infants reporting use of selected infant formula on at least one day of dietary recall; users percent represents weighted percent of the subpopulation.

Per user intakes of liquid milk solids from the intended use in infant formula were calculated from estimated intakes of energy as detailed above and in Table 7. Infants 3-5 months of age have the highest estimated intakes of liquid milk solids, with mean and 90th percentile intakes of 28 and 43 g/day, respectively. On a body weight basis, the highest estimated intake of liquid milk solids from the intended use in infant formula was among infants 0-2 months of age, with per user mean and 90th percentile intakes of 4.8 and 7.3 g/kg bw/day, respectively.

Table 8. Per user estimated daily intake of liquid milk solids from the intended use in infant formula, What We Eat In America/National Health and Nutrition Examination Survey (WWEIA/NHANES) 2011-2018

Age, months	Total Sample[a]	Users[b]		g/day[c]		g/kg bw/day[c]	
		Number	Weighted Percent	Mean	90th Percentile	Mean	90th Percentile
0-2	250	161	60.4	24	38	4.8	7.3
3-5	346	252	65.7	28	43	4.0	6.1
6-8	295	232	75.5	25	37	3.1	4.8
9-11	303	231	76.6	23	35	2.4	3.8

[a] Total sample represents unweighted number of infants with 2 days of recall data in the sample.
[b] Users number represents unweighted number of infants reporting use of selected infant formula on at least one day of dietary recall; users percent represents weighted percent of the subpopulation.
[c] Assumptions: 5.0 g liquid milk solids per 100 kcal infant formula powder; energy intake shown in Table 7.

3.2.4. Summary of Estimated Daily Intakes

Estimates of energy intake from select infant formulas representative of typical milk-based, 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 the intended use of liquid milk solids in infant formula. The intended use of up to 25 g liquid milk solids per 100 g infant formula powder corresponds to 5.0 g liquid milk solids per 100 kcal infant formula powder and 3.4 g liquid milk solids per 100 mL reconstituted infant formula.

Using WWEIA/NHANES 2011-2018 data, the estimated mean intake of energy from infant formula among consumers of infant formula was 490-558 kcal/day among infants in the first six months of life, and 452-502 kcal/day in the second six months of life. Based on energy intakes from formula and the intended use of liquid milk, the highest daily mean and 90th percentile intake of liquid milk solids by infants is among the subpopulation of infants 3-5 months of age with intakes of 28 and 43 g/day, respectively. The highest daily mean and 90th percentile intake of liquid milk solids on a body weight basis is among infants 0-2 months of age at 4.8 and 7.3 g/kg bw/day, respectively. Infant formula is formulated to provide complete and balanced nutrition for healthy term infants. In combination with other ingredients, the intended use of liquid milk will contribute to the total protein, fat, and carbohydrate content of the infant formula.

3.3. Nutrients in Liquid Milk and Maximum Allowable Levels in Infant Formula

As specified in 21 CFR §107.100, milk-based infant formulas are required to contain minimum levels of vitamins and minerals to ensure the infant formula provides adequate nutrients. For select micronutrients including vitamin A, vitamin D, iron, iodine, selenium, sodium, potassium,

and chloride, the regulations also specify maximum levels per 100 kcal infant formula (Table 9). The average concentration of these nutrients in liquid milk and the estimated concentration per 100 kcal infant formula powder provided by the intended use of liquid milk are summarized in Table 9 below, as well as the maximum concentration of each nutrient in liquid milk solids and the corresponding concentration per 100 kcal infant formula powder.

Table 9. Typical nutrient concentrations in liquid milk solids and potential concentration in infant formula vs maximum permitted concentration

Component	Unit	Average Nutrient Concentration in Liquid Milk		Maximum Nutrient Concentration in Liquid Milk		Maximum permitted level per 100 kcal (21 CFR §107)
		per 100 g liquid milk solids[a]	per 100 kcal infant formula powder[b]	per 100 g liquid milk solids[c]	per 100 kcal infant formula powder[b]	
Protein	g	22.0	1.1	23.3	1.2	4.5
Fat	g	20.6	1.0	21.8	1.1	6.0
Vitamin A	IU	690	34.5	1200	60	750
Vitamin D_3	IU	<270[d]	13.4	270[d]	14.0	100
Iron	mg	<0.34[d]	0.02	0.34[d]	0.02	3.0
Iodine	µg	40	2.0	190	9.5	75
Selenium	µg	7	0.4	35	1.8	7
Sodium	mg	191	9.6	380	19.0	60
Potassium	mg	841	42.1	1050	52.5	200
Chloride	mg	510	25.5	860	43.0	150

[a] Values represent average of samples from 4 non-consecutive batches of liquid milk calculated on a dry weight basis; see Table 6.
[b] Calculated values for the liquid milk component in infant formula assume 25 g liquid milk solids per 100 g infant formula powder, or 5.0 g liquid milk solids per 100 kcal infant formula powder.
[c] Values reflect maximum concentration per product specifications; see Table 5.
[d] Calculated from LOD for analysis in liquid milk (as is) and assuming the minimum concentration of solids (7.3 g per 100 g liquid milk). LOD per 100 g liquid milk (as is) is 20 IU [0.50 µg] for vitamin D_3 and 0.025 mg for iron; calculated LOD per 100 g liquid milk solids is 270 IU [6.8 µg] vitamin D_3, and 0.34 mg iron.

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 5, the maximum concentration of protein per 100 g of liquid milk is 23.3 g, and the maximum concentration of fat per 100 g of liquid milk is 21.8 g. At the maximum intended use of liquid milk in infant formula, liquid milk solids will account for no more than 1.2 g of protein per 100 kcal of infant formula powder and no more than 1.1 g of fat per 100 kcal (assuming 9 kcal per g of fat). These data demonstrate that at the maximum intended use of liquid milk, the naturally occurring levels of macronutrients and micronutrients observed in the liquid 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.

Part 4. Self-Limiting Levels of Use

The amount of liquid 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. The liquid milk that is the subject of this notice is for use as an ingredient in milk-based, non-exempt infant formula for healthy term infants at a maximum level of 25 g liquid milk solids 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 liquid milk as an ingredient in milk-based, non-exempt infant formula for healthy term infants is based upon scientific procedures.

Part 6. Narrative

6.1. Historical Use of Milk in Infant Formula

Human milk, which is recognized as the gold standard for infant feeding, provides a complex formulation of nutrients and non-nutritive bioactive substances that contribute to infant health (Dror & Allen, 2018). Infant formulas are used where human milk is not possible or desired and are therefore designed to replicate the compositional profile and mimic activity of human milk. Many infant formulas used in the first year of life are categorized as "milk-based". These formulas are traditionally manufactured from dry or liquid nonfat milk in combination with other milk-derived ingredients such as whey and lactose, which are the predominant sources of protein and carbohydrate, respectively. As previously described in several GRAS notices (e.g., GRN 898, GRN 980, and GRN 1041), infant formula in the U.S. has not typically made use of whole milk or milk fat, though cow milk, including evaporated milk and sweetened milk, have been used historically as substitutes for human milk and these formulations are recognized as the foundation for development of infant formula in the early 1900s (Innis, 2011; IOM, 2004; Jensen and Jensen, 1992). Originally, commercial milk-based infant formulas utilized a formulation called "synthetic milk adapted" and contained nonfat cow milk, lactose, and vegetable oils. Over time, adjustments were made to this cow milk base, including but not limited to modification of the fatty acid profile, dilution of protein, changes to the whey:casein ratio to mimic the ratio in human milk, and altering the micronutrient levels. Milk and milk products therefore have a long history of use in the U.S. food supply, including consumption by infants and also in the transition to a diet other than human milk or infant formula. Formulas produced from nonfat cow milk and milk-derived ingredients are still the primary source of nutrition for formula-fed infants in the U.S. (Corkins & Shurley, 2016; LSRO, 1998; Martin *et al*., 2016; Strzalkowski *et al*., 2022), though infant formula made with whole milk is available globally and has relatively recently entered the U.S. market. Throughout this dossier, reference to "milk" other than human milk refers to cow milk, which is referenced in some literature as bovine milk.

The intended use of liquid milk, composed of whole and nonfat milk in a combined form with lactose and water in approximate 4:1:1:4 proportions by weight, and pasteurized, will provide up to 25 g liquid milk solids per 100 g infant formula powder as an ingredient in milk-based, non-exempt infant formula for healthy term infants from the first day of life. Nonfat milk routinely has provided a source of high quality protein and some carbohydrate (lactose) when used as an ingredient in infant formula. Similarly, the intended use of liquid milk will provide high quality protein, carbohydrate (lactose), and fat that contribute to the overall nutrient profile of milk-based, non-exempt infant formula. The liquid milk ingredient will also provide relatively low concentrations of the vitamins and minerals naturally present in the constituent whole milk and nonfat milk components. Fortification of the final infant formula powder is necessary to achieve

established compositional requirements as set forth in U.S. regulations to ensure nutrient needs are met.

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

6.2.1. Regulatory Status in the United States

Milk-based infant formula is the most common type of infant formula used in the U.S. A variety of milk-derived ingredients are typically used in infant formula production, including nonfat milk (dry and liquid), whey protein concentrate, and lactose, all of which are recognized as GRAS for use in infant formula through common use prior to 1958 or a GRAS conclusion. At this time, several ingredients derived from cow milk, including dry whole milk, anhydrous milk fat (AMF), lactoferrin, and *Lactobacillus rhamnosus,* have been concluded to be GRAS for use in infant formula, FDA was notified of the GRAS conclusion, and FDA responded to each notice with a letter of "no questions". These GRNs are summarized in Table 10 below.

Table 10. GRAS notices (GRNs) for use of cow milk and cow milk-derived ingredients in infant formula

GRN No.	Substance	Intended Use	Date of Closure
1041	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 22% (w/w) powdered infant formula.	5/10/2022
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) 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	Cow milk-derived lactoferrin	Intended for use as an ingredient in cow 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 or prepared for consumption from powder or liquid concentrate), and in follow-on formula at a level of 15 mg/100 mL ready-to-feed or prepared for consumption from powder.	3/9/2017
465	Cow milk-derived lactoferrin	As an ingredient in cow milk-based term infant formulas at levels of 100 mg per 100 g powdered formulas, 26 mg per 100 mL liquid concentrates, and 13 mg per 100 mL ready-to-feed formula.	2/18/2014
281	*Lactobacillus rhamnosus* strain HN001 produced in a	Intended for use as an 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,	8/31/2009

GRN No.	Substance	Intended Use	Date of Closure
	milk-based medium	at a level of 10^8 colony forming units per gram of the formula powder.	

Liquid milk, which is composed of whole and nonfat milk in a combined form with lactose and water in approximate 4:1:1:4 proportions by weight, and pasteurized, is similar, though not identical, to the composition of dry whole milk GRAS ingredients (GRN 1041, GRN 980) which are a source of milk fat, protein, and carbohydrate. The fat component of liquid milk is likewise similar to the profile of AMF (GRN 980), which is a minimum of 99.8% milk fat.

GRN 1041 details the intended use of dry whole milk as an ingredient in milk-based, non-exempt infant formula for term infants, which was concluded to be GRAS at a maximum use level of 22 g per 100 g formula powder, or 4.3 g per 100 kcal infant formula based on a reconstitution rate of 13 g formula powder per 100 mL and an energy density of 67.6 kcal per 100 mL (Nara Organics, 2021). Nara Organics reported that the maximum intended use of dry whole milk is equivalent to 2.9 g dry whole milk per 100 mL infant formula as consumed with the dry whole milk providing 49% of protein, 21% of fat, and 16% carbohydrate in the total formula (GRN 1041, p.22 of 71).

GRN 980 details the GRAS intended use of dry whole milk as an ingredient in milk-based, non-exempt infant formula for term infants at a maximum level of 16 g per 100 g formula powder, or 3 g per 100 kcal infant formula based on a reconstitution rate of 12.5 g formula powder per 100 mL and an energy density of 67 kcal per 100 mL formula (ByHeart, 2020). ByHeart reported that the maximum intended use of dry whole milk contributes approximately 26% of the formula protein, 12% of the formula fat, and 8% of the formula lactose (carbohydrate) (GRN 980 amendment, p.4 of 52).

Prior to notification of these GRAS conclusions for the use of dry whole milk in infant formula, FDA was notified of the GRAS use of AMF in infant formula. GRN 898 details the intended use of AMF as a source of fat in milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants, with a maximum use level of 7% by weight of the fat blend in formulas containing up to 50% total energy as fat (Hogan Lovells, 2019). GRN 898 states that the maximum intended use of AMF provides an estimated 0.47 g AMF/kg bw/day, or up to 4.2 g AMF/day for an infant weighing up to 9 kg (GRN 898, p.30 of 121). The maximum intended use of AMF contributes approximately 0.39 g AMF per 100 kcal (GRN 898 amendment, p.20 of 65).

The maximum intended use of liquid milk, dry whole milk, and AMF, as well as the contribution of each ingredient to fat is summarized in Table 11 below. Based on the maximum intended use of 5.0 g liquid milk solids per 100 kcal, a mean concentration of 20.6 g fat per 100 g dry weight

of liquid milk solids (Table 6), and an assumption that fat accounts for 50% of total energy in the reconstituted infant formula and provides 9 kcal per g of fat, fat contributed by the liquid milk accounts for approximately 19% of total fat.[4]

Table 11. Maximum contributions of GRAS ingredients containing milk fat to total fat in infant formula

GRN No.	Substance and Intended Use	g ingredient per 100 kcal	g ingredient per 100 mL	% of total fat
Current	Liquid milk; maximum level of 25 g liquid milk solids per 100 g infant formula powder in milk-based, non-exempt infant formula for healthy term infants	5.0	3.4	19
1041	Dry whole milk; maximum level of 22% (w/w) in powdered infant formula in cow milk-based, non-exempt infant formula for term infants	4.3	2.9	21
980	Dry whole milk; maximum level of 16% (w/w) in powdered infant formula in cow milk-based, non-exempt infant formula for term infants	3.0	2.0	12
898	Anhydrous milk fat; maximum level of 7% of the fat blend in cow milk-based, calorically dense, ready-to-feed exempt infant formula for term infants	0.39	0.39	7

6.2.2. Whole Milk in Infant Formula Outside of the United States

Outside of the United States, formulas produced with whole milk and nonfat milk ingredients are available, including products marketed by Kendamil (United Kingdom), The a2 Milk Company (Australia), and Bellamy's Organic Infant Formula (Australia). The scientific literature also references infant formula containing milk lipids (e.g., Mendonça *et al*., 2017; Vandenplas *et al*., 2020), indicating that other products made with milk lipids may be consumed in many markets.

6.3. Approach for the Assessment of Safety for Milk Ingredients

The approaches employed for establishing safety of the intended use of ingredients delivering milk fat (i.e., dry whole milk and AMF) are relevant for the current assessment of the safety of the intended use of liquid milk. The use of dry whole milk, made from whole cow milk and meeting specifications as defined in GRN 1041 and GRN 980, was concluded to be safe for the intended use as an ingredient in infant formula at a maximum use level of 22 g per 100 g infant formula powder by Nara Organics (Nara Organics, 2021), and at a maximum level of 16 g per

4 $\frac{5.0\ g\ solids}{100\ total\ kcal}\ x\ \frac{20.6\ g\ milk\ fat}{100\ g\ solids}\ x\ \frac{9\ kcal}{g\ fat}\ x\ \frac{100\ total\ kcal}{50\ fat\ kcal} = \frac{9.27\ milk\ fat\ kcal}{50\ fat\ kcal} = 19\%\ kcal\ from\ milk\ fat\ kcal$

100 g infant formula powder by ByHeart (ByHeart, 2020). The use of AMF, made from cream or butter and meeting specifications as defined in GRN 898, was concluded to be safe for the intended use as an ingredient 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 (Hogan Lovells, 2019).

As discussed in GRN 1041 and GRN 980, multiple lines of evidence were reviewed to support the safety of the intended use of dry whole milk in infant formula, including: a summary of the known digestion of milk and principal milk components (i.e., protein, fat, carbohydrate), including potential differences in physico-chemical properties of unmodified milk, dry whole milk, and dry nonfat milk arising from processing to produce dry milk from fluid milk; a discussion of unmodified whole milk versus whole milk as a component in an infant formula formulation and potential physiological consequences; a discussion of the safety of consumption of components in whole milk that are not present in typical infant formula made with vegetable oils; a review of clinical studies in which infants consumed infant formula containing milk fat ingredients; and overall evidence supporting the absence of adverse effects in infants, children, and adults other than allergic reactions in certain individuals susceptible to milk allergies when milk is used as an ingredient. These reviews are provided in GRN 1041 on pp.32-42 and Appendix C, and in GRN 980 on pp. 20-27 and in the Amendment to GRN 980. GRN 898 (i.e., the intended use of AMF in select infant formula) also considered multiple lines of evidence to support the safety of AMF, including a review of the milk fat components not typical in formulas prepared with vegetable oils, and a review of clinical studies in which infants consumed milk fat (GRN 898, pp. 33-46). The present dossier is in agreement with the information summarized in GRN 1041, GRN 980, GRN 898, and the subsequent communications with FDA on these GRNs, and concurs that the intended uses of dry whole milk and AMF are GRAS.

The approach for determining safety of the intended use of liquid milk in milk-based, non-exempt infant formula for healthy term infants in this GRAS notice is reviewed below. Literature searches were conducted in PubMed to update the clinical evidence pertinent to the use of whole milk ingredients in infant formula products. A summary of the PubMed search strings and search dates used to identify literature for this review is provided in Appendix D. Additional searches, including searches of the FDA GRAS Inventory and general searches of the Internet, including reverse searches of key papers, were also conducted. The relevant recent literature identified in these searches was incorporated in the review below.

6.4. Digestion of Milk in Infant Formula

The liquid milk that is the subject of this GRAS notice is intended for use as an ingredient in milk-based, non-exempt infant formula, and as such will contribute to the overall nutrient profile of the final formulation. The intended use of liquid milk will contribute protein, fat, and lactose to the infant formula, along with relatively low concentrations of intrinsic micronutrients.

6.4.1. Protein

The liquid milk ingredient is manufactured using standard processes in the dairy industry. Milk proteins may be altered as a result of processing, and these changes in milk proteins may have physiological effects when consumed. The effects of processing, including a comparison between dry whole milk, dry nonfat milk and whole milk (unmodified) were most recently reviewed in GRN 1041 and a summary is presented below based on the review by van Lieshout *et al*. (2020) and the updated literature searches.

6.4.1.1. Heat Processing Effects

During standard dairy practices, milk proteins in general and the proteins in liquid milk undergo heat treatment. Pasteurization is a key heat processing step in the production of dairy products in general, and likewise is a step in the production of the liquid milk ingredient. Pasteurization is considered as a relatively mild heat treatment in dairy processing. While denaturation of whey proteins occurs during pasteurization, the extent of denaturation is limited to an estimated 5-15% of whey proteins (Deeth & Lewis, 2017). Process induced changes to protein in liquid milk that is the subject of this review would be similar to those resulting from the production of dry nonfat milk, dry whole milk, or liquid nonfat milk used in other infant formula powders.

The liquid milk is an integral part of a continuous process for manufacture of infant formula powder. Immediately following formation of the liquid milk, the liquid milk is delivered into mixing silos where other ingredients are added, and the resulting formulation is subsequently dried to produce the final infant formula powder. The drying process does not result in any significant further denaturation but does result in chemical modifications including glycation (known as the Maillard reaction) and oxidation (van Lieshout *et al*., 2020). These modifications, which may impact protein digestibility and amino acid availability, and therefore protein quality, also occur when infant formula is made with liquid or dry nonfat milk or dry whole milk.

Consistent with previous GRAS reviews, it is reasonable to conclude that the effects of processing on liquid milk have no meaningful impact on the safety profile relevant to different forms of milk used in infant formula. The intended use of liquid milk would be substitutional for other milk-based ingredients delivering protein in infant formula such as nonfat milk, dry whole milk, and whey powders. These ingredients, which are also subject to processing, have been used in infant formula for decades and are recognized as safe.

6.4.1.2. Potential Physiological Consequences

It is well known that milk proteins are highly digestible and thus a quality protein source for human nutrition. The modification of dairy proteins during standard processing, as described above, may affect protein digestibility or kinetics (van Lieshout *et al*., 2020, Bhat *et al*., 2021).

Two measures are commonly used to evaluate the nutritional quality of a protein source, namely the digestible indispensable amino acid score (DIAAS) and the protein digestibility amino acid score (PDCAAS). Nonfat milk powder, whole milk powder, and fluid milk have comparable PDCAAS and DIAAS scores, indicating comparable protein quality regardless of form thus the effect is minimal (Burd *et al*., 2019; FAO/WHO, 2013). Another measure used to assess the biological quality of protein is a protein efficiency ratio (PER) bioassay. Any non-exempt infant formulas marketed in the U.S. must meet the quality factor of sufficient biological quality of protein (21 CFR § 106.96(f)) by establishing the biological quality of the protein using an appropriate modification of the PER rat bioassay. Findings from a PER rat bioassay completed on a milk-based, non-exempt infant formula for healthy term infants containing liquid milk at the intended use level demonstrate that the protein in the formulation is of an appropriate biological quality for an infant formula.

6.4.1.3. Allergenicity

Milk is identified as one of the major food allergens in the U.S. Milk protein allergy is thought to affect around 2.6% of young children in North American population, with around 5-15% of infants experiencing intolerance to cow milk protein (Abrams & Sicherer, 2021; Corkins & Shurley, 2016). Infants who experience allergic reactions to cow milk-based formula are likely to be fed extensively hydrolyzed formulas or formulas containing non-milk sources of protein as an alternative to milk-based formulas.

6.4.1.4. Summary

Overall, as discussed by van Lieshout *et al*. (2020) in a discussion of 102 peer-reviewed articles and more recent literature (e.g., Li *et al.,* 2021, Bhat *et al*., 2021), milk processing may alter milk proteins in various ways and to different extents, which may result in altered protein digestibility and quality and other physiological consequences. The available data indicate that pasteurization and subsequent drying have limited effects on quality of protein in liquid milk. As described above, the liquid milk is processed under the same practices as those used in the processing of dry nonfat milk, dry whole milk, and whey powders commonly used as ingredients in infant formula and would be dried and stored during formula production similar to other forms of milk. Any differences between liquid milk, fluid whole milk, dry nonfat/whole milk, and unmodified milk are not expected to impact the safety profile of the ingredients.

6.4.2. Fat

The digestion of powder milk-based infant formulas with added milk fat has been compared with digestion of standard milk-based formula with vegetable fat and also human milk in several studies. Hageman and colleagues (2019a,b) used a static 2-phase *in vitro* digestion model to mimic gastric and duodenal phases of digestion, showing that human milk and powder based

infant formulas (presumably nonfat milk-based) and containing different fat blends, namely vegetable fat vs 33% vegetable fat with 67% bovine milk fat, exhibit similar release of total fatty acids as a percentage of the initial composition following digestion. When comparing the two formulas, differences in the release of some short- and medium-chain fatty acids were observed in the gastric and duodenal phases. However, at the end of total digestion, the formulas only differed by percentage of C14:0 released, with a lower percentage in the formula containing milk fat compared to the formula containing only vegetable fat.

Liu *et al*. (2021) also conducted an *in vitro* digestion model using human milk and infant formulas. Two infant formulas were prepared with whole bovine milk and whole goat milk, and two were prepared with nonfat milk (one with vegetable oils only and one with milk fat globule membrane (MFGM) and vegetable oils). Human milk had the highest lipolysis rate at 86.8%, the formula containing MFGM had a rate of 81.2%, formulas containing whole milk had rates of 78.0% (whole goat milk formula) and 77.6% (whole bovine milk formula), and the nonfat milk and vegetable oil based formula had the lowest rate of 70.5%. Following simulated intestinal digestion, palmitic acid levels from the formula containing a blend of whole bovine milk and vegetable fat and the formula containing only vegetable fat were comparable (235 and 251 μ mole/g, respectively).

A further study by Liu and colleagues (2022) compared *in vitro* digestion of human milk and infant formulas using a simulated model of infant gastrointestinal digestion. Five types of commercially available infant formulas were evaluated including two vegetable oil-based formulas (with and without MFGM) and three kinds of milk/vegetable oil-based formulas (i.e., with cream, with cream and soybean phospholipid, and with no supplement) and compared to human milk provided by healthy 10 Chinese females aged 18-30 years. The results showed rapidly increased particle size during gastric digestion in infant formula, which was significantly decreased during intestinal digestion. In contrast, the particle size in human milk increased slowly during gastric digestion, and then increased more rapidly during intestinal digestion. Human milk also had a very high lipolysis rate, which the authors suggested was due to the presence of MFGM. Following the simulated digestion, the proportion of saturated, monounsaturated and polyunsaturated fatty acids in digestion products of vegetable oil-based infant formulas were similar to that of human milk. Milk fat-based infant formula had significantly greater amounts of saturated fatty acids in digestion products than human milk, and all infant formulas had significantly lower levels of monounsaturated fatty acids in digestion products compared to human milk. The most abundant fatty acid released from human milk was C18:2n6c, while saturated fatty acids, such as C14:0, C16:0 and C18:0, were more abundant in infant formulas following intestinal digestion.

6.4.3. Carbohydrate

Like dry nonfat milk and dry whole milk, the liquid milk that is the subject of this GRAS notice will provide carbohydrate in the form of lactose. Lactose is known to be safe and is the major carbohydrate form in human milk (Kien, 1996), as well as an appropriate carbohydrate form in standard non-exempt infant formula (Corkins & Shurley, 2016; LSRO, 1998).

6.5. Unmodified Whole Milk vs Milk as an Ingredient

Use of evaporated milk or fresh cow milk were common infant feeding practices historically, however in the latter half of the 20th century evidence showed that unmodified whole milk was not appropriate as the sole source of nutrition for infants (Fomon, 2001; Ziegler, 2011). The liquid milk that is the subject of this GRAS notice will serve as one of the ingredients in the production of infant formula; the ingredient is not intended to be used as a sole source of nutrition for infants. As described in GRN 1041 (pp. 36-38), there are documented safety concerns in the literature regarding use of unmodified whole milk for infant feeding. These studies have been summarized below to address any potential concerns regarding the intended use of liquid milk as an ingredient in infant formula.

6.5.1. Nutrient Imbalances including Iron Deficiency

Iron deficiency is one potential adverse effect of consumption of fresh milk in infants. Studies on the consumption of fresh milk by infants have shown intestinal blood loss which may contribute to iron deficiency (Fomon, 1981; Wilson *et al*., 1974; Ziegler *et al*., 1990). However, Fomon and colleagues (1981) showed that consumption of milk which underwent processing, including time and temperature conditions similar to those used in the manufacture of standard infant formula, did not result in fecal blood loss. Therefore, a heat-sensitive protein likely plays a role in whole milk-induced bleeding. Other studies have shown similar results with heat-treated milk (Wilson *et al*., 1974). Studies have also shown that the youngest infants exhibit the greatest fecal iron loss, and this effect appears to be resolved by 12 months of age (Jiang *et al*., 2000; Ziegler *et al*., 1999). Additionally, fresh milk contains low concentrations of iron along with iron inhibitors such as calcium and casein, which may further contribute to iron deficiency following fresh milk intake in infants (Ziegler, 2011). In clinical studies, intake of fresh milk by infants results in early iron deficiency compared to consumption of a milk-based formula despite iron content being similar, suggesting that the effects are only of concern when fresh milk is consumed without further processing as part of an infant formula composition (Woodruff *et al*., 1972).

In the U.S., non-exempt infant formulas must contain 0.15 to 3.0 mg iron per 100 kcal (21 CFR §107.100). Any formula containing less than 1 mg of iron per 100 kcal requires a statement on the label noting that “Additional Iron May Be Necessary” to ensure infant iron needs are being

met. Other micronutrients found in low levels in milk also are required to be present in non-exempt infant formulas to ensure infant health (e.g., vitamin C, zinc, vitamin E, essential fatty acids). Infant formula made with liquid milk will meet all nutrient specifications for infant formula listed in 21 CFR §107.100.

6.5.2. Potential Renal Solute Load

Another concern for consumption of unmodified cow milk in infants is the risk of dehydration due to high potential renal solute load, especially during illness (LSRO, 1998). Conventional infant formula has a potential renal solute load of 20-26 milliosmole/100 kcal, which was concluded to be a satisfactory range (IOM, 2004; Ziegler and Fomon, 1989). The infant formula manufactured with liquid milk will deliver an appropriate renal solute load.

6.5.3. Avoiding Animal Fat

Some concerns have been raised with the use of animal fat such as butterfat (i.e., milk fat) in infant formula, on the premise that vegetable fats are preferential due to a variety of reasons, including but not limited to provision of higher concentrations of unsaturated fatty acids, avoidance of dioxins, reduction in the odor of regurgitated milk (due to removal of butterfat), and reduced cost (Hageman *et al*., 2019c).

Additionally, metabolic studies in infants have shown fecal fat loss with consumption of exclusively undiluted whole milk. Fomon and colleagues (Fomon *et al*., 1970) described studies in which infants were observed to excrete elevated levels of fecal fat following consumption of homogenized milk with 100% of fat as butterfat (milk fat). Consumption of evaporated milk resulted in ameliorated fecal fat loss compared to undiluted whole milk, while formulations containing milk as an ingredient, i.e., liquid or dry milk with added carbohydrate, did not result in fecal fat loss, thus suggesting no malabsorption had occurred. Fomon (1993) later described poor absorption of 100% milk fat in newborn infants. However, blends of 50% milk fat (providing approximately 25% of total energy assuming 50% energy from fat in the finished formula) and 50% vegetable oil (equal parts corn and coconut oil) in formula was well absorbed with excretion of fat being comparable to that resulting from consumption of human milk and infant formula. As previously noted, the fat from the intended use of liquid milk accounts for approximately 19% of total fat (Table 11); the amount of milk fat provided by the intended use of liquid milk does not present a safety concern since it is within the range of milk fat described in the literature as being well absorbed and is within the level of fat previously concluded to be GRAS.

6.6. Components in Liquid Milk Not Found Presently in Typical Formula

Cow milk contains lipids predominantly in the form of secreted globules from the mammary gland epithelial cells (Le Huërou-Luron *et al*., 2018). These globules are composed of a core containing triglycerides (~96-98%) and minor amounts of mono- and diglycerides and free fatty acids. The milk fat globule core contains a range of constituents, including carotenoids (mainly as beta-carotene), sterols mainly as cholesterol, fat soluble vitamins (A, E, D, and K), and flavor compounds (Mohan *et al*., 2020; Pacheco-Pappenheim *et al*., 2021). The globule core is surrounded by a tri-layer membrane known as the MFGM, which consists of a monolayer of polar lipids surrounded by a lipid bilayer with a glycosylated surface (Venkat *et al*., 2024). The MFGM, which accounts for approximately 1-6% of the total globule mass, is composed of lipids, membrane-specific proteins and enzymes (Mohan *et al*., 2020; Venkat *et al*., 2024). Approximately 60-70% of milk phospholipids in milk are in the MFGM, including glycerolphospholipids and sphingolipids as well as cholesterol (Contarini & Povolo, 2013; Mohan *et al*., 2020; Venkat *et al*., 2024).

Commercial infant formulas containing milk-derived ingredients provide exposure to milk fat components including short- and medium-chain fatty acids, branched- and odd-chain fatty acids, trans fatty acids, conjugated linoleic acid (CLA), as well as phospholipids, cholesterol and sphingolipids since these formulas are estimated to contain up to 4% residual milk fat (Berger *et al*., 2000, Jensen *et al*., 1991; Gallier *et al*., 2020, Byrne *et al*., 2021). These milk fat constituents also are present in varying concentrations in human milk, thus infants are routinely exposed to these substances. Analytical data on the concentration of these constituents in liquid milk are summarized below along with data on the concentration of the constituents in human milk. Data on the concentration of these constituents in dairy fats and human milk were adapted from extensive reviews presented in the GRAS notices for AMF (GRN 898) and dry whole milk (GRN 1041).

6.6.1. 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, CLA, 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 liquid milk intended for use as an ingredient in milk-based, non-exempt infant formula was examined and results are summarized in Table 12.

Table 12. Typical concentrations of fatty acids and cholesterol in liquid milk, per 100 g liquid milk solids

Component[a]	Unit	Batch #1487322	Batch #1556448	Batch #1627984	Batch #1628829
4:0 Butyric acid	mg/100 g, dry wt	562	668	667	718
Trans fatty acids[b]	g/100 g, dry wt	<1.3	<1.3	1.3	1.4
18:2 Conjugated linoleic acid	mg/100 g, dry wt	161	187	173	149
15:0 Pentadecanoic acid	mg/100 g, dry wt	228	214	293	257
17:0 Heptadecanoic acid[c]	mg/100 g, dry wt	<137	<137	<137	<137
Cholesterol[d]	mg/100 g, dry wt	84	63	68	68

[a] Fatty acids analyzed AsureQuality method (based on JAOCS, 62(1985)).
[b] *Trans* fatty acids, acid form; limit of detection (LOD) < 0.1 g/100 g liquid milk (as is). Values in 100 g dry wt calculated from LOD in liquid milk (as is) and reported solids for each sample.
[c] Heptadecanoic acid; LOD < 10 mg/100 g liquid milk (as is). All values in liquid milk (as is) were reported as <LOD. Value in 100 g dry wt calculated from LOD in liquid milk (as is), and assuming the minimum concentration of solids (7.3 g per 100 g liquid milk).
[d] Cholesterol analyzed with method AOAC 933.08, 970.50, 970.51 (Table 5).

Assuming the maximum intended use of liquid milk in milk-based, non-exempt infant formula (25 g liquid milk solids per 100 g infant formula powder), mean concentrations of these fatty acids and cholesterol from liquid milk were estimated and the percent of total fatty acids in the infant formula was approximated (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 milk fat also are present in human milk, and in varying concentrations in infant formulas prepared from a variety of fat sources. For all components, the intended use of liquid milk results in concentrations of these components well within or below the range of mean concentrations typically reported in human milk.

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

Component	mg per 100 g liquid milk solids[a]	Calculated mg per 100 mL infant formula[b]	Calculated % of fatty acids in 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 acid	654	22	0.58	0.0009-0.76	ND-3.1
Trans fatty acids	1.3	0.05	1.2	1.9-2.7	ND-1.56
18:2 Conjugated linoleic acid	168	5.7	0.15	0.07-0.49	ND-0.33
15:0 Pentadecanoic acid	248	8.4	0.22	0.08-0.50	ND-0.6
17:0 Heptadecanoic acid	<137	<4.7	<0.12	0.19-0.41	ND-0.4
Cholesterol	71	2.4	-	9-20 mg per 100 mL	1.46-5.1 mg per 100 mL

[a] Values represent average of 4 samples from non-consecutive batches of liquid milk, calculated on a dry weight basis (see Table 12).
[b] Shown as liquid milk contribution to infant formula under the intended use. Calculated values in infant formula assume 3.4 g liquid milk solids per 100 mL reconstituted infant formula.

[c] Shown as liquid milk contribution to infant formula fatty acid profile under the intended use. 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 [from GRN 1041, Table 13]).
[e] 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 [from GRN 1041, Table 13]); ND – not detected.

6.6.2. Phospholipids

Milk fat is a source of phospholipids including phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and sphingomyelin. The concentrations of phospholipids in liquid milk intended for use as an ingredient in milk-based, non-exempt infant formula were measured and reported in Table 14 below. The predominant phospholipids are phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin, which is consistent with the concentration of phospholipids reported in dry whole milk (Soga *et al*., 2015).

Table 14. Typical concentrations of phospholipids in liquid milk, per 100 g liquid milk solids

Component[a]	Unit	Batch #1487322	Batch #1556448	Batch #1627984	Batch #1628829
Phosphatidylcholine	mg/100g, dry wt	56	43	51	47
Phosphatidylethanolamine	mg/100g, dry wt	60	39	43	50
Phosphatidylinositol	mg/100g, dry wt	16	9	13	16
Phosphatidylserine	mg/100g, dry wt	27	20	19	24
Total sphingomyelin[b]	mg/100g, dry wt	47	43	39	37
Total phospholipid[c]	mg/100g, dry wt	214	164	171	180

[a] Phospholipid content was analyzed by ^{31}P NMR analysis (MacKenzie *et al*., 2009).
[b] Total sphingomyelin includes sphingomyelin and dihydrosphingomyelin.
[c] Total phospholipid includes lysophosphatidylcholine and lysophosphatidylethanolamine.

Based on the maximum intended use of liquid milk in infant formula and compositional data on phospholipids in liquid milk (Table 14), the concentration of phospholipids provided by the intended use of liquid milk in infant formula was estimated (Table 15). Table 15 also provides reported data on concentrations of phospholipids in human milk for comparison. These data indicate that the estimated concentration of phospholipids from the intended use of liquid milk 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 liquid milk with comparison to concentrations in human milk

Component	mg per 100 g liquid milk solids[a]	Calculated mg per 100 mL infant formula[b]	Reference values mg per 100 mL human milk[c]
Phosphatidylcholine	49	1.7	3.3
Phosphatidylethanolamine	48	1.6	7.0

Component	mg per 100 g liquid milk solids[a]	Calculated mg per 100 mL infant formula[b]	Reference values mg per 100 mL human milk[c]
Phosphatidylinositol	14	0.5	0.8
Phosphatidylserine	22	0.8	3.8
Total sphingomyelin[d]	41	1.4	6.2
Total phospholipid[e]	182	6.2	21.6

[a] Values represent average of 4 samples from non-consecutive batches of liquid milk, calculated on a dry weight basis (see Table 14).
[b] Shown as liquid milk contribution to infant formula under the intended use. Calculated values in infant formula assume 3.4 g liquid milk solids per 100 mL reconstituted infant formula.
[c] 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.
[d] Total sphingomyelin includes sphingomyelin and dihydrosphingomyelin.
[e] Total phospholipid includes Lys phosphatidylcholine and lysophosphatidylethanolamine.

6.7. Consumption of Milk Fat by Infants in Infant Formula

The intended use of liquid milk as an ingredient in milk-based, non-exempt infant formula will provide a source of protein, fat, and carbohydrate (lactose) from dairy sources. Milk-based infant formulas have relied on dairy sources of protein and carbohydrate from ingredients including nonfat milk, lactose, and whey powder ingredients for decades and use of these ingredients is recognized as safe. Use of dairy ingredients that provide fat also have been recognized as safe, including use of dry whole milk, corresponding to up to 16% (GRN 980) or up to 21% (GRN 1041) of the total fat in the final formula. In GRN 898, the use of AMF as a source of fat in cow milk-based, calorically dense, ready-to-feed and exempt infant formula for term infants accounts for up to 7.0% by weight of the fat blend in formulas containing up to 50% of energy as fat. As shown in Table 11, the intended use of liquid milk will provide up to 19% of total fat, which is a level of milk fat within the range recognized as safe.

To support the safety of milk fat in infant formula, clinical studies in which milk fat provided a source of fat in infant formula were critically reviewed. Literature searches conducted for GRN 1041 identified 4 published clinical trials in which a source of cow milk fat was included in infant formula and provided up to 50% of total fat (Breij *et al*., 2019; de Souza *et al*., 2018 and Leite *et al*., 2013; Manios *et al*., 2020 [two trials]). GRN 898 identified a trial in which infant formula with an unspecified level of milk fat was compared to formula made with vegetable oils (Gianni *et al*., 2018a and Gianni *et al*., 2018b). All forms of milk fat provided a source of the fatty acids found in fluid or dry whole milk, though AMF provides little or no components located in the MFGM (Huppertz & Kelly, 2006). As summarized in GRN 1041 and 980, these trials provide evidence that infant formulas with milk fat providing up to 50% of the fat blend support infant growth and are well tolerated.

The more recent literature also was reviewed for studies examining infants consuming formula made with milk fat compared with infants consuming formula made with vegetable oils. Studies comparing formula made with cow milk fat and other animal sources of fat (e.g., goat milk [Jung *et al*., 2023]) were not considered relevant for this review. Four additional clinical studies were identified in which cow milk fat contributed to the fat blend and measures of adverse events or growth and tolerance were compared to measures in infants consuming formula made with vegetable oil (Kuehn *et al.,* 2022; Looijesteijn *et al*., 2022; Nomayo *et al*., 2020 and Lambidou *et al*., 2021; Vandenplas *et al*., 2020). Two of these trials provided 50% of fat in infant formula as milk fat (Looijesteijn *et al*., 2022; Vandenplas *et al*., 2020). The amount of fat provided as milk fat was not specified in two studies, one of which was a growth monitoring study sponsored by ByHeart, Inc., the Notifiers of GRN 980 (Kuehn *et al*., 2022), and one of which was a 12-week intervention designed to examine effects of galacto-oligosaccharides (GOS) in combination with milk fat on measures of gut microbiota and infant health (Nomayo *et al*., 2020 and Lambidou *et al*., 2021).

Collectively, the findings from these clinical trials overall provide supportive evidence that growth is supported when milk fat is used as a component of up to 50% of the fat blend in infant formula, and that formula made with milk fat is well tolerated by infants. These studies therefore support the intended use of up to 25 g liquid milk solids per 100 g infant formula powder, accounting for 19% of total fat as milk fat based on representative product data.

6.8. Consumption of Whole Milk by Infants

Clinical studies in which infants and young children consumed bovine whole milk or bovine milk fat were identified and summarized in GRN 980 and GRN 1041 and are incorporated herein by reference. A total of 23 studies were cited in GRN 980 and GRN 1041, including 8 prospective interventions in infants, of which 7 were repeat intake studies with durations between 6 days and one year and 1 examined acute effects of milk consumption. As described in previous sections of this dossier, Fomon and colleagues (1981) and Ziegler and colleagues (1990) reported that consumption of fluid pasteurized milk may contribute to iron deficiency in infants and is therefore not recommended. However, milk which underwent processing with time and temperature conditions similar to those used in infant formula production did not result in fecal blood loss, unlike unmodified cow milk (Fomon *et al*., 1981). The liquid milk ingredient will not be provided as a sole source of nutrition. The presence of whole milk in the liquid milk ingredient does not present safety concerns associated with consumption of whole milk by infants.

6.9. GRAS Criteria and Conclusion

6.9.1. 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.

6.9.2. GRAS Conclusion

The substance that is the subject of this GRAS notice is liquid milk, composed of whole and nonfat milk in a combined form with lactose and water in approximate 4:1:1:4 proportions by weight, and pasteurized. The intended use of liquid milk is as an ingredient in milk-based, non-exempt infant formula for healthy term infants at a maximum level of 25 g liquid milk solids per 100 g infant formula powder.

The liquid milk that is the subject of this notice is produced from milk and lactose in addition to water. Monitoring data on the incoming milk demonstrate compliance with standards that ensure

its safety as a food ingredient, and the lactose meets food-grade specifications for the intended use. The liquid milk is manufactured using standard dairy processing steps under conditions of current good manufacturing practices (cGMP). The liquid milk is an integral part of a continuous process for manufacture of infant formula powder. Immediately following the formation of the liquid milk, the liquid milk is delivered into mixing silos where other ingredients are added simultaneously, and the resulting formulation is subsequently dried to produce the final infant formula base powder.

Milk and milk products have a long history of use in the U.S. food supply, including consumption by infants. Milk-based infant formulas are the most common type of infant formula used in the U.S. A variety of milk-derived ingredients are typically used in infant formula production, including nonfat milk (dry and liquid), whey protein concentrate, and lactose, all of which are recognized as GRAS for use in infant formula through common use prior to 1958 or a GRAS conclusion. Milk ingredients recognized as GRAS for use in select infant formulas that provide a source of milk fat include use of dry whole milk (GRN 1041, GRN 980) and anhydrous milk fat (GRN 898), with these sources providing up to 22% of total fat as milk fat; SML concurs with these GRAS conclusions. The intended use of liquid milk in this notice, at a maximum level of 25 g liquid milk solids per 100 g infant formula powder, represents a level of milk fat within the range previously concluded to be safe in the evaluation of the safety of the intended uses of dry whole milk and AMF. A similar approach therefore was employed to evaluate the safety of the intended use of liquid milk.

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

Potential concerns with the consumption of fluid whole milk as a sole source of nutrition for infants (e.g., potential nutrient deficiency, potential renal solute load; fat absorption) have been raised in the literature. Liquid milk is intended for use as an ingredient in milk-based, non-exempt infant formula and not direct consumption, thus it provides a portion of nutrients as part of a formulation designed to meet nutrient needs. With the exception of the well-documented occurrence of allergic reactions in susceptible individuals (Abrams & Sicherer, 2021), milk and milk products ingredients in infant formula have been consumed with no adverse effects attributable to the milk.

The use of liquid milk in infant formula will provide a source of constituents typically present in lower concentrations in formula, namely select fatty acids and cholesterol and phospholipids

present in milk fat and not present in vegetable oils. The level of these components provided by the intended use of liquid 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 clinical studies in which milk fat accounts for up to 50% of the fat in infant formula (Breij *et al*., 2019; De Souza *et al*., 2017; Leite *et al*., 2013; Kuehn *et al.,* 2022; Lambidou *et al.* 2021; Manios *et al*., 2020 (two trials); and Nomayo *et al*., 2020) provide supportive evidence that the level of milk fat provided by the intended use of liquid milk does not present safety concerns. The use of commercially available infant formulas in markets including Australia and the United Kingdom that contain liquid milk as a source of nutrients in the formulation also provides corroborative support regarding the safety of liquid milk as an ingredient.

6.9.3. 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 liquid 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 applicable to liquid milk. The data and publicly available information supporting the safety of the proposed use of liquid 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 intended use of liquid milk as an ingredient in milk-based, non-exempt infant formula for healthy term infants at a maximum concentration of 25 g liquid milk solids per 100 g infant formula powder can be concluded to be safe and GRAS through scientific procedures.

6.9.4. Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the intended use of liquid milk as an ingredient in milk-based, non-exempt infant formula for healthy term infants, 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

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Appendices

Appendix A. Raw Materials Used to Produce the Liquid Milk

Incoming Milk: Monitoring Data

Monitoring data on the incoming raw milk demonstrate that mycotoxins (Table A1), environmental contaminants (Table A2), veterinary drug residues (Table A3), and pesticide residues (Table A4) demonstrate compliance of the incoming raw milk with requirements of the 2019 Pasteurized Milk Ordinance (PMO) in the United States, and thus the incoming milk is suitable for the intended use.

Aflatoxin M1

Table A1. Aflatoxin M1 monitoring data demonstrating consistency of the incoming raw milk with the PMO

Component	SML Specification	SML Monitoring Data 2018-23 (Avg)[a]	National Monitoring Data[b]	U.S. Limits[c]
Aflatoxin M1	<0.05 µg/L	< 0.050 µg/L	< 0.050 µg/L	0.5 ppb (0.5 µg/L)

[a] SML monitors aflatoxin M1 in incoming milk; results from 370 samples.
[b] New Zealand Dairy NCCP (National Chemical Contaminants Programme); Maximum value is equivalent to EU action levels. No. of samples = 3,784 between 2014/15 and 2021/22, none of which were above action or maximum levels.
[c] Reference for U.S. Limits: CPG 527.400 (action level for aflatoxin M1).

PCBs, Dioxins and Furans, Radionucleotides

Table A2. Environmental contaminant monitoring data demonstrating consistency of the incoming raw milk with the PMO

Component	SML Specification	SML Monitoring Data 2018-23 (Avg)[a]	National Monitoring Data[b]	U.S. Limits[c]
Non dioxin like PCBs (ndl PCBs), sum of	-	-	<2.00 pg/g fat	1.5 ppm (fat basis) (1,500,000 pg/g)
Sum WHO(2005)-PCDD/F + dl-PCBs TEQ (upper bound)	<5.3 pg/g fat	1.1 pg/g fat	<5.5 pg/g fat	-
Dioxins and Furans WHO (2005)-PCDD/F TEQ (upper bound)	<5.3 pg/g fat	0.53 pg/g fat	< 1.75 pg/g fat	-
Activity Iodine 131	<2.0 Bq/kg MS	0.74 Bq/kg MS	<2.0 Bq/kg MS	170 Bq/kg
Activity Caesium 134	<2.0 Bq/kg MS	1.03 Bq/kg MS	<2.0 Bq/kg MS	1200 Bq/kg
Activity Caesium 137	<2.0 Bq/kg MS	1.07 Bq/kg MS	<2.0 Bq/kg MS	1200 Bq/kg

Abbreviation: MS – milk solids.
[a] SML monitors PCBs, dioxins and furans, and radionucleotides in incoming milk; results represent values from a biannual sampling plan.
[b] New Zealand Dairy NCCP (National Chemical Contaminants Programme) Maximum value is equivalent to EU action levels. No samples detected exceeding EU action or maximum levels. No. of samples = 3,784 between 2014/15 and 2021/22 none of which were above action or maximum levels.

[c] Reference for U.S. Limits: 21 CFR 109.30 (tolerances for PCBs); CGP 555.880 (guidance levels for radionucleotides).

Animal Drugs

Table A3. Veterinary drug residue monitoring data demonstrating consistency of the incoming raw milk with the PMO

Component	SML Specification	SML Results[a]
Beta-lactam + non-beta lactam antibiotics	<0.003 IU/mL	<0.003 IU/mL
Beta-lactam antibiotics	Not Detected	Not Detected

[a] Raw fluid milk is monitored for the presence of beta-lactam antibiotics and non beta-lactam antibiotics per the New Zealand Dairy NCCP (National Chemical Contaminants Programme). At SML, each tanker load of milk is checked and passed for beta-lactam residues prior to unloading (Charm – KIWI strip test). Each farm tested 3 x per month by independent laboratory Delvotest T (combined beta- & non beta- lactams). The NCCP screens individual farm milk supplies for evidence of a range of antimicrobial compounds including penicillins, cephalosporins, aminoglycosides, macrolides, tetracyclines and a sulphonamide, using a four-plate microbial inhibition test (coded as MIT) and Delvotest T. The Delvotest T method has been verified in New Zealand milk for ampicillin, cephalonium, cloxacillin, gentamicin, oxytetracycline, sulfadiazine and tylosin. Tetracyclines are also tested using a SNAP test. Confirmation testing is undertaken for any presumptive positive results.

Pesticides

Table A4. Pesticide residue monitoring data demonstrating consistency of the incoming raw milk with the PMO

Component	NCCP Action limit (mg/L)[a]	Limit of Detection (mg/L)	Monitoring Data	U.S. limits[b]
Aldrin & Dieldrin	0.006	0.002	<LOD	0.3 ppm
Benzene Hexachloride (BHC)	0.005	0.002	<LOD	0.3 ppm
DDT, DDE, & TDE	0.02	0.002	<LOD	1.25 ppm
Heptachlor & Heptachlor Epoxide	0.004	0.002	<LOD	0.05 ppm
Lindane	0.002	0.002	<LOD	0.3 ppm

[a] New Zealand Dairy NCCP National Chemical Contaminants Programme (Raw Milk), July 2021 to June 2022. Action limits in milk are established for all residues of primary interest in the NCCP (National Chemical Contaminants Programme). Where maximum residue levels have been set, the action limit is typically the lowest value applied under New Zealand, Codex or importing country MRLs. Where a compound is not permitted, or not registered for use on milking animals, the action limit is at the laboratory method reporting limit.
[b] Reference for U.S. Limits: CPG 575.100 (action levels for pesticides).

Lactose

To Whom It May Concern:

This letter is written to confirm that Cheese, Whey Protein, Lactose, and products bearing the Hilmar Cheese Company and Hilmar Ingredients label are produced exclusively at the Hilmar Cheese Company dba Hilmar Ingredient sites in Hilmar, California, USA and Dalhart, Texas, US. Hilmar Cheese Company and Hilmar Ingredients are hereinafter referred to as HCC.

HCC the manufacturer declares that:

- Hilmar Lactose products are compliant with the General Food definition referenced in 21 CFR 168.122 for Lactose.

If you have any questions, please feel free to contact me.

Best Regards,

Gabriela Araujo
Corporate Quality Assurance
Hilmar Cheese Company, Inc. / Hilmar Ingredients

Review Date: 3/23/2023
Revised Date: 3/23/2023

Headquarters & Innovation Center
8901 North Lander Avenue, P.O. Box 910, Hilmar, CA 95324 USA T: 209.667.6076 Fax: 209.634.1408 hilmarcheese.com

California Manufacturing Site & Visitor Center: 9001 North Lander Avenue, P.O. Box 910, Hilmar, CA 95324 USA T: 209.667.6076
Texas Manufacturing Site: 12400 US Highway 385, P.O. Box 1300, Dalhart, TX 79022 USA T: 806.244.8800

HILMAR INGREDIENTS®

CERTIFICATE of ANALYSIS

SYNLAIT MILK LIMITED

Customer Material Number: 300014
Customer PO: 1100000229- 1

Sales Order: 376456
Manifest: 80427928

Qty: 1
Units: EA

Lot No: 1402041
Part Number: 300014
Product Name: 5000 EDIBLE LACTOSE 1000KG

Manufacture Date:
August 01,2022

Expiration Date:
July 31,2024

Characteristic	Unit	Lower Limit	Upper Limit	Test Value
ASH	%	0.000	0.300	**0.174**
COLIFORM	cfu/g	0	10	**<10**
MOISTURE	%	0.00	0.50	**0.11**
LACTOSE PURITY	%	99.00	100.00	**99.66**
LISTERIA GENUS @25G	-	-	-	**Negative**
MOLD	cfu/g	0	50	**<10**
PH		4.50	7.00	**5.55**
PROTEIN	%	0.00	0.60	**0.05**
SALMONELLA @25G	-	-	-	**Negative**
SCORCH	-	-	-	**7.5mg**
STANDARD PLATE COUNT	cfu/g	0	10000	**<250**
STAPH	cfu/g	0	10	**<10**
YEAST	cfu/g	0	50	**<10**
NITRATE	ppm	0.00	50.00	**4.01**
NITRITE	ppm	0.00	2.00	**0.07**
FAT - PERIODIC TEST	%	-	-	**<0.50**
KARL FISCHER - PERIODIC TEST	%	-	-	**<6.000**

Note:ISSUED BY MANUFACTURER

Manufactured By:

Hilmar Ingredients
9001 North Lander Avenue
Hilmar,CA, 95324

[redacted]

Griselda Garcia
Corporate Quality Assurance Manager

Date:11/03/2022

COA Issued by Manufacturer

1402041 - 1

Appendix B. WWEIA/NHANES 2011-2018 Infant Formula Food Codes 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)
11710482	Similac Go and Grow, infant formula, prepared from powder, made with tap water
11710484	Similac Go and Grow, infant formula, prepared from powder, made with baby water
11710621	Infant formula, ready-to-feed (Enfamil Newborn)
11710626	Infant formula, powder, made with water, NFS (Enfamil Newborn)

Food Code	Food Description
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)
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)
11710640	Enfamil PREMIUM LIPIL, infant formula, NS as to form
11710643	Enfamil PREMIUM LIPIL, infant formula, prepared from powder, made with water, NFS
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
11710647	Enfamil PREMIUM LIPIL, infant formula, prepared from powder, made with tap water
11710648	Enfamil PREMIUM LIPIL, infant formula, prepared from powder, made with plain bottled water
11710649	Enfamil PREMIUM LIPIL, infant formula, prepared from powder, made with baby water
11710650	Enfamil LIPIL, infant formula, NS as to form
11710651	Enfamil LIPIL, infant formula, ready-to-feed
11710653	Enfamil LIPIL, infant formula, prepared from powder, made with water, NFS
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
11710657	Enfamil LIPIL, infant formula, prepared from powder, made with tap water
11710658	Enfamil LIPIL, infant formula, prepared from powder, made with plain bottled water
11710659	Enfamil LIPIL, infant formula, prepared from powder, 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)

Food Code	Food Description
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)
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)
11710930	Infant formula, NS as to form (Gerber Graduates Gentle)
11710937	Gerber Good Start 2 Gentle Plus, infant formula, prepared from powder, made with tap water
11710938	Gerber Good Start 2 Gentle Plus, infant formula, prepared from powder, made with plain bottled water
11710949	Gerber Good Start 2 Protect Plus, infant formula, prepared from powder, made with baby water
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)
11720323	Infant formula, powder, made with water, NFS (Enfamil Enfagrow Toddler Transitions Soy)
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)

Food Code	Food Description
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)
11720628	Gerber Good Start 2 Soy Plus, infant formula, prepared from powder, made with plain bottled water
11720629	Gerber Good Start 2 Soy Plus, infant formula, prepared from powder, made with baby water
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)
11740311	Infant formula, ready-to-feed (Enfamil Nutramigen)
11740312	Infant formula, liquid concentrate, made with water, NFS (Enfamil Nutramigen)
11740313	Infant formula, powder, made with water, NFS (Enfamil Nutramigen)
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)
11740329	Enfamil Nutramigen AA LIPIL, infant formula, prepared from powder, made with baby water
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. Clinical Studies of Infants Consuming Formula with Milk Fat vs Formula Containing Plant Fats

Reference	Duration and Intervention	Adverse Events/ Growth & Tolerance Outcomes	GRAS Review
Kuehn *et al*., 2022 Sponsored by ByHeart, Inc.	Multisite, randomized, double-blind, controlled, non-inferiority trial 211 healthy, singleton, term infants aged ≤ 14 days at enrollment randomized to consume a test or control formula for 24 weeks; study included a human milk reference group: o Test: Infant formula (ByHeart) made with **whole milk; level not specified** (n=106, 61 per protocol completers) o Control: commercial formula (Enfamil); contained skim milk (n=105, 67 per protocol completers) o Reference: Human milk (n=100, 57 per protocol completers)	**Adverse Events** - Occurrence of possibly related AEs by organ systems and use of concomitant medications similar between groups; gastrointestinal disorders most frequent, with 8 in test group, 6 in control group. **Growth & Tolerance** - No differences in weight-for-age, length-for-age, head circumference-for-age, and weight-for-length z-scores between the test and control groups; non-inferiority was demonstrated. - Lower formula intake by body weight and decreased protein intake in the test group compared to control group. - No differences in mean number of stools per day, occurrence of moderate or excessive gas, level of fussiness, or hours of crying per day between groups. Softer mean stool consistency in test group and fewer mean number of spit-ups over time in the test group compared to the control group.	Current GRAS review
Looijesteijn *et al*., 2022 Sponsored by Friesland-Campina Nederland B.V.	Single-blind, randomized, crossover, placebo-controlled trial 22 healthy term infants, formula-fed, aged 9-16 weeks at enrollment randomized to consume a test or control formula for 2 weeks followed by a crossover to the other formula; no washout period (19 completers): o Test: Infant formula with fat as **50% milk fat** and 50% vegetable fat	**Adverse Events** - No AEs or SAEs were reported during the study for any of the groups. **Growth & Tolerance** - Infant weight and length development during the study and average weekly infant formula intake were similar for the test and control groups.	Current GRAS review

Reference	Duration and Intervention	Adverse Events/ Growth & Tolerance Outcomes	GRAS Review
	○ Control: Infant formula with vegetable fat	- No significant differences between group in vomiting, regurgitation, colic, constipation, diarrhea and crying episodes. No differences in stool volume or color were observed between the two groups.	
Nomayo *et al*., 2020; Lambidou *et al*., 2021 Sponsored by Humana GmbH/ DMK Baby, Germany	Double-blind, randomized controlled trial 94 healthy infants aged ≤ 10 days at enrollment randomized to consume a test or control formula for 12 weeks; study included a human milk reference group: ○ Test: Infant formula with a blend of fat from **milk fat (unspecified amount)**, vegetable, and fish oil (20–25% beta-palmitic acid) and GOS (0.5 g GOS/100 mL) (n=47, 30 per protocol completers) ○ Control: Infant formula with a blend of fat from vegetable and fish oil (<10% beta-palmitic acid) (n=47, 27 per protocol completers) ○ Reference: Human milk (n=34, 18 per protocol completers)	**Adverse Events** - No SAEs reported in either the test or control groups. **Growth & Tolerance** - No differences in mean weight gain, mean length grain, mean head circumference growth, and mean formula intake between test and control groups after 12 weeks. - No differences in the number of respiratory and/or gastrointestinal infections between any of the groups after 12 weeks.	Current GRAS review
Vandenplas *et al*., 2020 Sponsored by Danone Nutricia Research, Utrecht, The Netherlands	Double-blind, randomized, controlled, multi-country, parallel trial 215 healthy term infants, formula-fed, aged ≤ 14 days at enrollment randomized to consume a test or control formula to age 17 weeks; study included a human milk reference group: ○ Test: Infant formula made from partly fermented milk with a blend of fat from **49.8% AMF** and vegetable oils and added short-chain GOS/long-chain FOS (9:1) and 2'-FL (n=108, 90 completers)	**Adverse Events** - No differences in any SAEs between the test and control groups: 11 SAEs including system organ class of infection and infestation, infantile vomiting, and Rhesus incompatibility, all non-related or unlikely related to the study product, were reported in 5.6% of infants in the test group and 3.8% of infants in the control group. **Growth & Tolerance** - Equivalence in weight, length, and head circumference gain between the test and control groups was observed.	Current GRAS review

Reference	Duration and Intervention	Adverse Events/ Growth & Tolerance Outcomes	GRAS Review
	○ Control: Infant formula made with vegetable fat and added short-chain GOS/long chain-FOS (9:1) (n=107, 86 completers) ○ Reference: Human milk (n=61, 56 completers) *Test product had higher amounts of ARA and DHA (16.5 mg) than the control (10-11 mg)	- No differences in gastrointestinal tolerance between the test and control groups; overall both formulas were well-tolerated.	
Manios *et al*., 2020 Sponsored by Friesland-Campina Nederland B.V.	Double-blind, randomized, crossover, placebo-controlled trial 17 healthy term, formula-fed infants, aged 9-14 weeks randomized to consume a test or control formula for 2 weeks followed by a crossover to the other formula; no washout period (16 completers): ○ Test: Infant formula with fat as **50% milk fat** and 50% vegetable fat ○ Control: Infant formula with vegetable fat	**Adverse Events** - No information provided. **Growth & Tolerance** - No differences in formula intake, weight, or length measurements. - Decreased stool consistency and more reports of watery stools compared to vegetable fat control.	GRN 1041, pp. 70-71
Manios *et al*., 2020 Sponsored by Friesland-Campina Nederland B.V.	Double-blind, randomized, crossover, placebo-controlled trial 18 healthy term, formula-fed infants, aged 9-14 weeks randomized to consume a test or control formula for 2 weeks followed by a crossover to the other formula; no washout period (17 completers): ○ Test: Infant formula with **20% milk fat** and 80% vegetable fat ○ Control: Infant formula with vegetable fat	**Adverse Events** - No information provided. **Growth & Tolerance** - No differences in formula intake, weight, or length measurements between the test and control groups. - No differences in stool consistency between the test and control groups.	GRN 1041, pp. 70-71
Breij *et al*., 2019	Double-blind, randomized, controlled, multi-country, (growth) equivalence trial 223 healthy term infants, formula-fed, aged ≤ 35 days at enrollment randomized to consume a test	**Adverse Events** - No differences in any AEs/SAEs between the test and control groups with the exception of a lower percentage of	GRN 1041, p. 70 GRN 898, Table 9

Reference	Duration and Intervention	Adverse Events/ Growth & Tolerance Outcomes	GRAS Review
Sponsored by Nutricia Research Related papers with efficacy outcomes: Schipper *et al*., 2023; Abrahamse-Berkeveld *et al*., 2024	or control formula to age 17 weeks; study included a human milk reference group: ○ Test: Infant formula with fat as **48% dairy lipid**; blend with plant oils; larger diameter lipid droplets with milk phospholipid coating; increased sn-2 palmitic acid content (n=115, 87 completers) ○ Control: Infant formula with plant oils (n=108, 81 completers) ○ Reference: Human milk (n=88, 69 completers)	subjects with dry skin in the test (0.9%) compared with the control group (6.8%). **Growth & Tolerance** - No differences in weight, length, or head circumference gain, and weight-for-age, length-for-age, head circumference-for-age z-scores between the test and control groups. Lower weight-for-length z-scores in test group compared with control at weeks 13 and 17. - 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. - Increased 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.	
Gianni *et al*., 2018a; Gianni *et al*., 2018b Sponsored by Lactalis Nutrition Europe, Torcé, France	Double-blind, randomized, controlled, monocentric, parallel trial 88 healthy term infants, aged ≤ 3 weeks at enrollment randomized to consume a test or control formula for 4 months; study included a human milk reference group: ○ Test: Infant formula with **milk fat (amount not specified;** source of dairy fat assumed to be cream based on product label for Milumel, the formula used in the study); blended with plant oils (n=30, 23 completers) ○ Controls: Infant formula with plant oils (n=28, 24 completers) or plant oils with ARA and DHA (n=30, 23 completers) ○ Reference: Human milk (n=29, 19 completers)	**Adverse Events** - Adverse events were recorded throughout the study period but results not reported in paper. Rates of discontinuation reported to be similar in 3 formula groups; gastrointestinal symptoms were the most common reason for study discontinuation. **Growth & Tolerance** - No differences in gains of weight, length, or head circumference or fat mass among formulas. - No differences in gastrointestinal parameters, gastrointestinal symptoms, or infant behavior.	GRN 898, Table 9

Reference	Duration and Intervention	Adverse Events/ Growth & Tolerance Outcomes	GRAS Review
de Souza *et al*., 2017; Leite *et al*., 2013 Sponsored by Abbott Nutrition and Abbott Laboratories	Double-blind, randomized, crossover, controlled balance trial 33 healthy term infants, aged 68-159 ± 3 days at enrollment randomized to consume a test or control formula for 2 weeks (tolerance phase) + 4 days (metabolic phase) followed by a crossover to the other formula; no washout period (32 completers): o Test: Infant formula with fat as **2.8% milk fat** and plant oils, including ARA and DHA o Control: Infant formula with plant oils, including ARA and DHA	**Adverse Events** - No differences in any AEs/SAEs between the test and control groups. **Growth & Tolerance** - Increased stool frequency and percentage of formed stools with consumption of the test formula during the metabolic phase; no difference during tolerance period. No effect on formula intake. - No differences in occurrence of spit-up/vomit, fussiness and gassiness in the test group compared to the control group.	GRN 1041, p. 70 GRN 898, Table 9

Abbreviations: 2'-FL – 2'-Fucosyllactose; AEs – Adverse Events; AMF – anhydrous milk fat; ARA – arachidonic acid; DHA – docosahexaenoic acid; FOS – fructo-oligosaccharides; GOS – galacto-oligosaccharides; SAEs – Severe Adverse Events.

Appendix D. PubMed Literature Searches

No.	Search String	Hits	Date
1	(bovine OR cow OR dairy) AND ("milkfat" OR "whole milk" OR "butterfat" OR "milk powder" OR "evaporated milk" OR "condensed milk" OR fat OR lipid) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: (("2021/06/01"[Date - Publication] : "3000"[Date - Publication]))	282	June 19, 2023
2	(bovine OR cow OR dairy) AND ("protein*" OR amino OR peptide) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: Meta-Analysis, Review, Systematic Review, English, from 2021/6/1 - 3000/12/12	82	June 19, 2023
3	(bovine OR cow OR dairy) AND ("milkfat" OR "whole milk" OR "butterfat" OR "milk powder" OR "evaporated milk" OR "condensed milk" OR fat OR lipid) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: English, from 2023/6/1 - 3000/12/12	73	October 25, 2023
4	(bovine OR cow OR dairy) AND ("protein*" OR amino OR peptide) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: Meta-Analysis, Review, Systematic Review, English, from 2023/6/1 - 3000/12/12	9	October 25, 2023
5	(bovine OR cow OR dairy) AND ("milkfat" OR "whole milk" OR "butterfat" OR "milk powder" OR "evaporated milk" OR "condensed milk" OR fat OR lipid) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: English, from 2023/10/1 - 3000/12/12	52	January 15, 2024
6	(bovine OR cow OR dairy) AND ("protein*" OR amino OR peptide) AND (infant OR baby OR pediatric OR paediatric OR neonate OR newborn OR infant formula) Filters: Meta-Analysis, Review, Systematic Review, English, from 2023/10/1 - 3000/12/12	14	January 15, 2024
7	process* AND ("milk protein*" OR "dairy protein*") Filters: Review, English, from 2021/6/1 - 3000/12/12	69	January 15, 2024

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
001172	Feb 22, 2024
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

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

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

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

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

3 Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* 2023/05/31

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

SECTION B – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position or Title
Caroline Gain	Head of Global Regulatory Affairs

Organization *(if applicable)*: Synlait Milk Limited

Mailing Address *(number and street)*: 1028 Heslerton Road

City	State or Province	Zip Code/Postal Code	Country
Rakaia	Canterbury	7783	New Zealand

Telephone Number	Fax Number	E-Mail Address
0064277064769		caroline.gain@synlait.com

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

Name of Contact Person	Position or Title
Mary Murphy	Principal Scientist

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

Mailing Address *(number and street)*: 1150 Connecticut Avenue, NW, Suite 1100

City	State or Province	Zip Code/Postal Code	Country
Washington	District of Columbia	20036	United States of America

Telephone Number	Fax Number	E-Mail Address
202-772-4953		mmurphy@exponent.com

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

liquid milk, composed of whole & nonfat milk in a combined form with lactose & water (approx 4:1:1:4 wt proportions), & pasteurized

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

☒ Electronic Submission Gateway ☐ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

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

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

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

☒ a) GRAS Notice No. GRN 1041

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☒ e) Other or Additional *(describe or enter information as above)* GRNs 980 and 898

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

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

7. Does the submission (including information that you are incorporating) contain information that you view as trade secret or as confidential commercial or financial information? (see 21 CFR 170.225(c)(8) and 170.250(d) and (e))

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

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

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

☐ No

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

☐ Yes, a redacted copy of the complete submission

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

☐ No

SECTION D – INTENDED USE

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

The intended use of liquid milk is as an ingredient in milk-based, non-exempt infant formula for healthy term infants at a maximum level of 25 g liquid milk solids per 100 g infant formula powder.

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

(Check one)

☐ Yes ☒ No

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

(Check one)

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

SECTION E – PARTS 2 -7 OF YOUR GRAS NOTICE

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

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

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

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

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

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

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

Other Information

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

☐ Yes ☒ No

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

☐ Yes ☐ No

SECTION F – SIGNATURE AND CERTIFICATION STATEMENTS

1. The undersigned is informing FDA that Caroline Gain
(name of notifier)

has concluded that the intended use*(s)* of liquid milk, composed of whole & nonfat milk in a combined form with lactose & water (approx
(name of notified substance)

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

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

Exponent, Inc., 1150 Connecticut Avenue, NW, Suite 1100, Washington, DC 20036
(address of notifier or other location)

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

3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
Caroline Gain Digitally signed by Caroline Gain Date: 2024.02.22 16:50:19 +13'00'	Caroline Gain, Head of Global Regulatory Affairs	02/22/2024

SECTION G – LIST OF ATTACHMENTS

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

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	LiquidMilkGRASDossier.pdf	Submission

From: Mary Murphy
To: Morissette, Rachel
Subject: [EXTERNAL] RE: questions for GRN 001172
Date: Tuesday, April 23, 2024 4:05:56 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image005.png
image006.png
2302253.000 - 8289_Liquid Milk_responses on GRN 1172.pdf

Hi Rachel,

Please find attached responses to the questions on GRN 1172. If you have additional questions, please reach out.

Thank you,
Mary

From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Monday, April 15, 2024 2:25 PM
To: Mary Murphy <mmurphy@exponent.com>
Subject: [EXTERNAL] questions for GRN 001172

Hi Mary,

Please see attached our questions for GRN 001172.

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION


I GOT MY
COVID-19
VACCINATION

Responses to questions on GRN 1172

Regulatory:

1. On p. 32, Synlait states "The fat component of liquid milk is likewise similar to the profile of AMF (GRN 980), which is a minimum of 99.8% milk fat." We note that GRN 000898 was for the use of AMF, not GRN 000980.

Response: We acknowledge our error in referencing the GRN for use of AMF. The sentence should read as follows: "The fat component of liquid milk is likewise similar to the profile of AMF (GRN 898), which is a minimum of 99.8% milk fat."

Chemistry:

2. On p. 18, Table 5 lists a specification limit for *Cronobacter* species of not detected in 100 g, as is, and states that the method used is ISO 22964-2017. We note this method recommends a sample size of 10 g. Please clarify whether Synlait has validated this method for a sample size of 100 g.

Response: ISO 22964:2017 has been validated for test portions of 10 g. However, the method (Section 10.1) notes that both smaller (<10 g) or larger (>10 g) test portions may be used. A smaller test portion may be used without the need of additional validation/verification providing that the same ratio between pre-enrichment broth and test portion is maintained. A larger test portion may be used if validation/verification has been completed to show no negative effects on the detection of *Cronobacter* spp.

The Synlait Milk Ltd microbiology laboratory is IANZ (International Accreditation New Zealand) accredited. The laboratory has verified the test method (ISO 22964:2017) for test sample portions of 10 g and up to but not exceeding 300 g over a range of dairy ingredients and finished products. The laboratory confirms that for all production batches submitted in the GRAS notification, a 100 g test portion was weighed out and added to 900 mL of the pre-enrichment medium (buffered peptone water) creating a ten-fold dilution in accordance with ISO 22964:2017 Section 10.1.

Toxicology:
3. On p. 34, Synlait states "The present dossier is in agreement with the information summarized in GRN 1041, GRN 980, GRN 898, and the subsequent communications with FDA on these GRNs, and concurs that the intended uses of dry whole milk and AMF are GRAS."

As noted in Table 11 on p. 33, the intended use of AMF in GRN 000898 is specifically for "calorically dense, ready-to-feed exempt infant formula for term infants," which is different from the use in GRN 001172 (i.e., non-exempt infant formula). Given that a GRAS conclusion is specific to the intended use, please clarify that the data and information discussed in GRN 000898 still supports the safe use of liquid milk blend in non-exempt infant formula.

Response: The data and information in GRN 898 support the safe use of AMF in "calorically dense, ready-to-feed exempt infant formula for term infants" when used at a level of up to 7% of the fat blend, which corresponds to 0.39 g AMF per 100 kcal and 0.39 g AMF per 100 mL. As noted in GRN 898 (p. 30), "The nutrient dense formula in which AMF is intended to be used as a component of the fat blend is a high-energy formulation intended for use in term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism. Term infants consuming the calorically dense formula with AMF would reasonably digest and metabolize triglycerides as do other term infants consuming human milk or standard infant formula." The conclusion of safety of the intended use of AMF was based on an evaluation of data and information comparing constituents in AMF and constituents in human milk. The safety assessment in GRN 898 was additionally supported by evidence from clinical studies documenting that formulas containing milk fat were well tolerated by infants and the formulas supported growth.

The conclusions of safety of the intended uses of dry whole milk (GRN 1041, GRN 980) and liquid milk (filed as GRN 1172) were likewise based on evaluations of data and information comparing constituents in whole milk and constituents in human milk, and GRN 1172 and GRN 1041 also included supportive evidence from clinical studies documenting that formulas containing milk fat were well tolerated by infants and the formulas supported growth. Comparisons between constituents in milk fat and human milk made in these GRAS notices (898, 980 1041, 1172) draw upon some of the same data from the published literature.

Table 11 in the current GRAS notice summarizes the maximum contributions of GRAS ingredients containing milk fat to infant formula macronutrient composition. Based on the maximum fat content of each ingredient, the maximum use level of each ingredient, and the per user estimated 90th percentile energy intake, the maximum intake of milk fat from the intended use of each ingredient was calculated; these intakes are summarized in Table 1 below. These data demonstrate that the intended uses of the milk fat containing ingredients provide a range of milk fat intake for the target populations of infants. The conclusion of safety for the intended use of liquid milk as documented in this notice (GRN 1172) is consistent with the conclusion of safety for the intended use of AMF.

Table 1. Intake of milk fat from the intended uses of milk fat containing ingredients in infant formula

GRN No.	GRAS Ingredient Maximum Intended Use					Maximum kcal intake/ day	Maximum g milk fat intake/ day	Data Sources [b]
	g per 100 kcal	g per 100 mL	% milk fat [a]	% of total fat in infant formula	g milk fat per 100 kcal			
1172	5.0	3.4	21.8	19	1.1	860	9.4	Product specifications in Table 5 in the GRN (p. 18 of 73); EDI in Table 7 (p. 25 of 73), kcal/day for infants aged 3-5 months at the 90th percentile
1041	4.3	2.9	35	21	1.5	833	12.5	Product specifications in Table 6 in the GRN (p. 18 of 71); EDI in Table 8 (p. 24 of 71), kcal/day for infants aged 3-5 months at the 90th percentile
980	3.0	2.0	40	12	1.2	733	8.8	Product specifications in Revised Table 2 in the amendment (p. 11 of 52; numbered p. 9); EDI of 141 kcal/kg bw/day at the 90th percentile in the GRN (p. 14 of 40, numbered p. 13), and interpolated 90th percentile weight for males at age 1 month (5.2 kg = average of 0.5 and 1.5 month values; https://www.cdc.gov/growthcharts/percentile_data_files.htm)
898	0.39	0.39	99.9	7	0.4	907	3.5	Product specifications in Table 3 in the GRN (p. 23 of 121, numbered p. 16); EDI of 144 kcal/kg bw/day at the pseudo-90th percentile in Table 3 in the supplemental correspondence (p. 41 of 65, numbered p. 24) and interpolated 3rd percentile weight for males at age 6 months (6.3 kg = average of 5.5 and 6.5 month values; https://www.cdc.gov/growthcharts/percentile_data_files.htm)

[a] Maximum milk fat value represents upper range of fat component in the GRAS ingredient for GRN 1172, GRN 1041, and GRN 980. Value represents the average fat value in GRN 898.

[b] Page numbers correspond to pages within the PDF files unless otherwise noted.

Toxicology (continued):

4. On p. 47, Synlait states "The use of commercially available infant formulas in markets including Australia and the United Kingdom that contain liquid milk as a source of nutrients in the formulation also provides corroborative support regarding the safety of liquid milk as an ingredient."

The assumption from this statement is that there have been no reports of adverse effects attributed to the use of liquid milk blend in these formulas already consumed by infants in Australia and the United Kingdom. Please confirm this assumption is correct.

Response: The use of liquid milk in New Zealand is common practice and we are not aware of adverse effects from this practice. We confirm the assumption that we are not aware of reports of adverse effects attributed to the use of liquid milk in these formulas in Australia and the United Kingdom.