February 16th, 2023

Regarding: GRAS Notice Dry Whole Goat Milk

FDA,

Jovie is pleased to notify the agency of its conclusion that Dry Whole Goat Milk (DWGM) is safe as an ingredient for non-exempt infant formulas; a conclusion supported by the determination of a panel of scientists (Expert Panel) convened to review the evidence and reasoning that form the basis of Jovie's conclusion.
Jovie convened the Expert Panel in advance of FDA's *Best Practices for Convening a GRAS Panel: Guidance for Industry Guidance on GRAS panels (Dec 2022)*; however, Jovie applied the principles enumerated in the draft Guidance in most regards. Jovie did not have a written GRAS Panel policy, but in written manner or orally in initial group meetings Jovie related the key elements of a GRAS panel policy.

In particular, as described in more detail below:

1. We determined whether or not there was a need for an Expert Panel.
2. We were careful in the recruitment of scientists to the Expert Panel to establish balance and avoid bias.
3. We documented the absence of conflicts of interest by each member.
4. The chair of the Expert Panel was selected in part because of his extensive work on previous Expert Panels that provided him an understanding of the Expert Panel process, and proved competence with processes that minimize the risk of bias.
5. Jovie and a consultant on regulatory processes provided technical input and clarifications but had no voice in decision making.

Ad 1. The need for an Expert Panel
Jovie determined that an Expert Panel review was necessary and sufficient because there was considerable peer-reviewed scientific literature pertaining to goat milk in infant formula, but the composition, including ingredient specifications, of the goat milk preparations used in the literature were not exactly the same as the proposed ingredient. The most important information on the use of whole goat milk in infant formula is a review by the European Food Safety Authority and the clinical study it was based on reported by Zhou *et al.* (2014). Additionally, some clinical studies used preparations of goat milk protein or combinations of goat milk protein preparations, not whole goat milk powder. Indeed, there is a previous GRAS notification Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate (GRN 644) that includes the goat milk protein source Jovie has determined to be safe, but in GRN 644 the nonfat dry goat milk powder is used in combination with goat milk whey concentrate. Finally, in a meeting with the infant formula team at FDA in Nov 2021, Jovie was encouraged to submit a GRAS notification for DWGM. Importantly, there are no severe conflicts among scientists about the safety of DWGM.

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Ad 2. Care in the recruitment of scientists to the Expert Panel to establish balance and avoid bias.
Jovie consulted with Dr Roger Clemens to chair the Expert Panel, and to develop panel membership. Scientists were sought with expertise in physical, chemical, and biologic properties of foods that could be brought to bear on DWGM. Jovie included persons with expertise in food toxicology, food technology, dietary exposure, food allergy, pediatric gastroenterology, pediatric nutrition, and regulatory governance. Because the intended use was non-exempt infant formula, Jovie emphasized persons experienced in conduct of clinical trials with infants, physicians specialized in pediatric medicine, and experts in pediatric nutrition. Some members had some previous experience in GRAS Expert Panels. The number of members was larger than most expert panels, not because the subject was contentious, but to emphasize the breadth of general acceptance.

Ad 3. Documented the absence of conflicts of interest by each member.
None of the panel members had any financial relationship with Jovie; a statement of (lack of) conflict of interest was obtained from each panel member. A modest honorarium was specified at the outset of the relationship.

Ad 4. The chair of the Expert Panel
Dr Clemens has served on dozens of GRAS expert panels. His background and work experience include lead roles for an infant formula company entering the US market, presidency of Institute of Food Technologists, membership in the American College for Toxicology, and university level teaching of regulatory science. He has been a reviewer or editor for more than 30 professional journals or government grants. This experience makes him exquisitely aware of the need to present information factually without bias. Dr Clemens actively encouraged members to offer contrasting points of view. The lively discussion during group zoom meetings is a credit to his ability to balance the need to hear and respect all perspectives and still move forward on the agenda. Because of the open nature of the discussion, Dr Clemens volunteered on a few occasions that this Expert Panel was the finest of any on which he has served.
Most of the group work was done by zoom. Email with/without attachments was generally sent to all panel members at the same time, in some instances clarifications or additional data were sent in response to individual panelist's questions during redrafting, and the redrafted text was reviewed subsequently by the full panel.

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Ad 5. Technical input and clarifications
Jovie's head of R&D, Henrike Wemekamp, PhD, with assistance of regulatory consultant John Wallingford, PhD, drafted the GRAS notification that was shared with the Expert Panel, and provided all the referenced literature and unpublished data for the Panelist's consideration. Dr Wemekamp provided unpublished data on the composition of DWGM. The initial draft text was comprehensive in citation of scientific literature pertaining to goat milk. Some sections of the initial text were considered by the panel to be not relevant to the determination of safety of the ingredient in infant formula, e.g., history of consumption of goat milk as a food, effects of processing other than that used to produce the ingredient, and by consensus were deleted.

Yours faithfully,

Mrs. Henrike Wemekamp-Kamphuis, PhD
Manager Research & Development
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Generally Recognized as Safe (GRAS) Determination for the Intended Use of Dry Whole Goat Milk in Non-exempt Infant Formula

Prepared by:

Jovie USA, LLC.

Rolling Meadows, Illinois, USA

January, 2023

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PART 1. Signed Statements and Certification

Pursuant to 21 CFR Part 170, subpart E, Jovie USA LLC (hereinafter referred to as 'Jovie') submits a Generally Recognized as Safe (GRAS) notice and claims that the use of Dry Whole Goat Milk as the source of protein in infant formula for full-term gestation infants (>37 weeks of gestational age) up to 12 months of age, as described in Parts 2 through 7 of this GRAS notice, is not subject to premarket approval requirements of the FD&C Act based on its conclusion that the substance is GRAS under the conditions of its intended use.

1.A. Name and Address of the Notifier

Contact: Mrs. Henrike Wemekamp-Kamphuis, PhD

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As the Notifier, Jovie USA LLC accepts responsibility for the GRAS determination that has been made for Dry Whole Goat Milk meeting the conditions described herein, is exempt from pre-market approval requirements for use as a food ingredient in full-term gestation infants up to 12 months of age.

1.B. Common or Trade Names

The official nomenclature according to Title 21 sec. 131.147 is 'Dry Whole Goat Milk'. The common name for the substance of interest is 'Whole Goat Milk Powder' (WGMP), also referred to as 'Full cream goat milk powder' in countries outside the USA. The trade name of the ingredient is Green Goat® Full cream goat milk powder.

It is a homogeneous, off-white, free flowing powder that is obtained by the removal of water from fresh goat milk. It contains lactose, milk proteins, milkfat, and milk minerals in the same relative proportions as the milk from which it was made. It contains not less than 26 percent but less than 40 percent by weight of milkfat on an as is basis. It contains not more than 5 percent by weight of moisture on a milk solids not fat basis.

1.C. Applicable Conditions of Use of the Notified Substance

Jovie USA LLC intends to use Dry Whole Goat Milk (DWGM) as a food ingredient in non-exempt infant formulas (term infants; ages from birth to 12 months). The DWGM will serve as the protein source in ready-to-drink or powdered forms of infant formulas from which reconstituted infant formulas can be prepared.

1.D. Basis for the GRAS Determination

This GRAS conclusion is based on scientific procedures in accordance with 21 CFR 170.30(a) and 170.30(b).

1.E. Availability of Information

The data and information underlying this GRAS conclusion will be made available to FDA upon request by contacting H. Wemekamp-Kamphuis at Jovie USA LLC at the above address. The data and information will be made available to FDA in a form in accordance with that requested under 21 CFR 170.225(c)(7)(ii)(A) or 21 CFR 170.225(c)(7)(ii)(B).

1.F. Availability of FOIA Exemption

None of the data and information in Parts 2 through 7 of this GRAS notice is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. §552.

1.G. Certification

We certify that, to the best of our knowledge, this GRAS conclusion is based on a complete, representative, and balanced dossier that includes all relevant information, available and obtainable by us, including any favorable or unfavorable information, and relevant to the assessment of the safety and GRAS status of the use of Dry Whole Goat Milk (DWGM).

1.H. Name, Position, and Signature of Notifier

Mrs. H.H. Wemekamp-Kamphuis, PhD
Manager Research & Development
Jovie USA LLC

1.I. FSIS/USDA Statement

Jovie USA LLC does not intend to add Dry Whole Goat Milk to any meat and/or poultry products under USDA jurisdiction. Therefore, 21 CFR 170.270 does not apply.

PART 2. Identity, Methods of Manufacture, Specifications, and Physical and Technical Effects

2.A. Identity of the Notified Substance

Dry Whole Goat Milk (hereinafter referred to as 'DWGM') is similar to its cow milk counterpart Dry Whole Milk (also referred to as full cream milk powder), which is included in FDA's food standards for milk and cream products (21 CFR 131.147, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=131.147), being described as 'Dry whole milk is the product obtained by removal of water only from pasteurized milk, as defined in 131.110 (a), which may have been homogenized. It contains lactose, milk proteins, milkfat, and milk minerals in the same relative proportions as the milk from which it was made. It contains not less than 26 percent but less than 40 percent by weight of milkfat on an as is basis. It contains not more than 5 percent by weight of moisture on a milk solids non-fat basis. This section of the regulation further notes that the addition of vitamins A and D is optional, along with carriers for these vitamins, emulsifiers, stabilizers, anticaking agents, and antioxidants. The DWGM that is the subject of this GRAS document does not contain added vitamins A or D or any of the other optional ingredients identified above for dry whole milk.

2.B. Method of Manufacture

The DWGM is produced using standard dairy processing techniques with purely mechanical procedures as shown in Figure 1. No component of DWGM is concentrated to more than naturally occurring levels. The DWGM is produced from goat milk in processing plants that apply Hazard Analysis Critical Control Point (HACCP) plans and current Good Manufacturing Practices as the basis for certification by FSSC 22000 (Food Safety System Certification), IFS (International Featured Standard), or BRC (British Retail Consortium) food safety standards.

Farms mainly use goats of the Swiss breed Saanen. Before processing, the raw goat milk is analyzed with Charm MRL (Maximum Residue Limits) to ensure the absence of antibiotic residues (detection of 14 common beta-lactams at or below European Union (EU) Maximum Residue Levels (MRL), including cloxacillin, ceftiofur, cefalonium, and cefquinome). The milk is pasteurized (≥72°C, 15 seconds), cooled, and stored at ≤6°C until further processing (within 48 h). This pasteurization is a Critical Control Point and is fully controlled. An evaporator is then used to concentrate the milk. The goat milk concentrate is further dried using a spray dryer. The water content of the goat milk is reduced to ≤5%, rendering powdered goat milk. This dried goat milk is sieved (2 mm; 10 mesh), and subsequently packed per 25 kg in food-grade bags conforming to FDA CFR Title 21, Part 175-178. The packaged product is checked with a metal detector after packing (the metal detector is tested with Fe: 3.0 mm, non-Fe: 3.5 mm, and 3.5 mm stainless steel).

The end product is extensively analyzed to ensure compliance with the specification (Tables 1 and 2). Analyses include moisture, fat, protein, ash, titratable acid, and insolubility. Microbiological analyses include total plate count, coliforms, yeasts and molds, *Bacillus cereus*, coagulase positive staphylococci, salmonella, listeria, clostridia, and cronobacter.

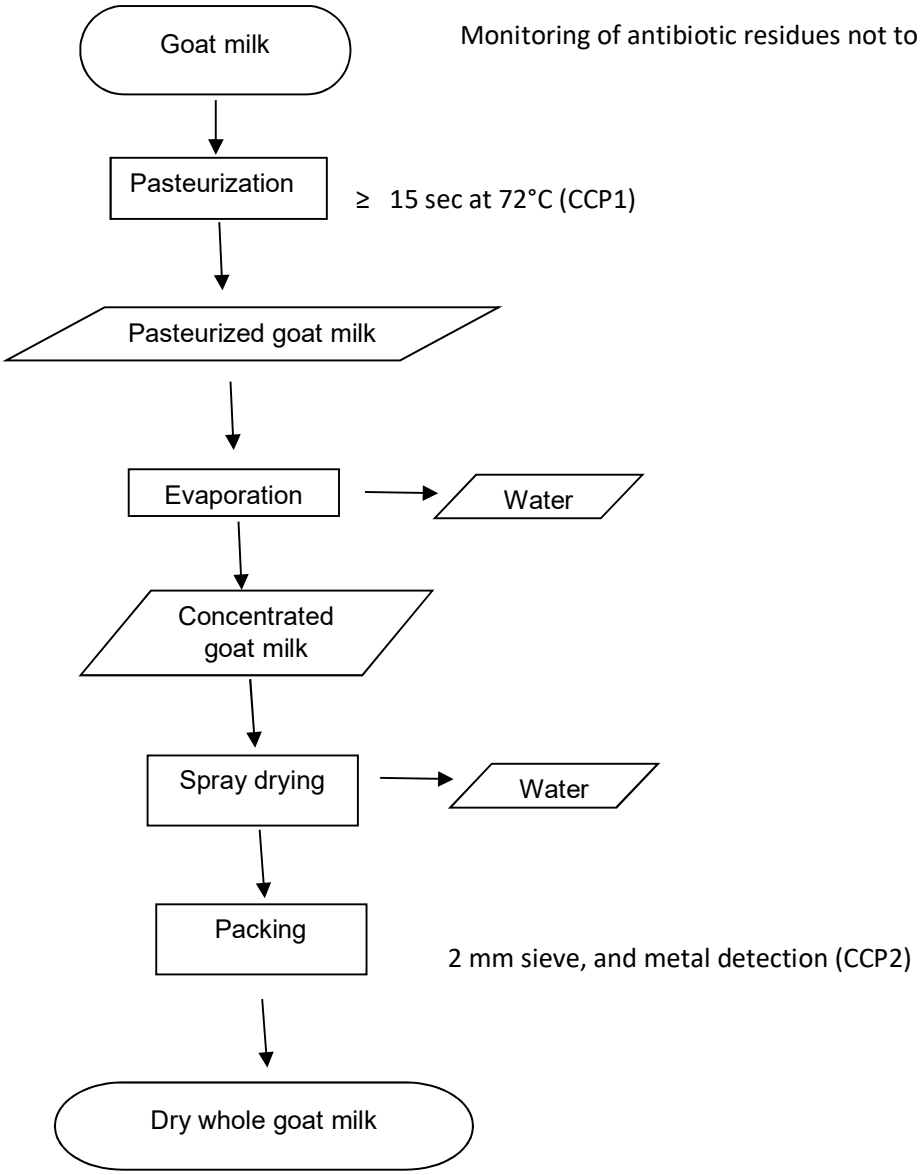

Figure 1. *Process Flow Diagram of Dry Whole Goat Milk.*

2.C. Specifications and Composition

As described above, dry whole milk from bovine sources is included in FDA's food standards for milk and cream products (21 CFR 131.147), with a set minimum percent of milkfat and maximum percent of moisture on a milk solids non-fat basis. Information presented in Table 1 demonstrates that DWGM complies with the specifications for dry whole milk sourced from bovine milk, as well as additional parameters described in Codex Standard 207-1999 for milk powders and cream powder.

***Table 1**. Comparison of Dry Whole Goat Milk Specifications with FDA (21 CFR 131.147), Codex, and/or European Standards for Dry Whole Milk.*

Parameter	Specification Standard		Dry Whole Goat Milk			Method
	Value	Reference	Minimum	Typical	Maximum	
Milkfat (% w/w)	Min 26% Max 40%	21 CFR 131.147	26	32	35	ISO 1736 (IDF 9:2008)
Moisture (% w/w in milk solids non-fat)	≤ 5 %	21 CFR 131.147	na[1]	1.5	5	ISO 5537
Milk protein (% m/m in milk solids not-fat, N*6.38)	≥ 34 %	Codex Standard 207-1999	34	39	Not applicable	ISO 8968-1:2014 (IDF20-1:2014)
Titratable acidity (ml 0.1N NaOH/10g solids-not-fat)	≤ 18 %	Codex Standard 207-1999	na[1]	12	18	ISO 6091 (IDF 86:2010)
Scorched particles[2]	Max Disc B	Codex Standard 207-1999	na[1]	A	B	ISO 5739 (IDF 107:2003)
Solubility index (ml)	Max 1	Codex Standard 207-1999	na[1]	0.1	1	ISO 8156
Heavy Metals						
Lead (mg/kg)	< 0.15	Codex Standard 193-1995	na[1]	< 0.02	< 0.15	ICP-MS (ANA-130)
Cadmium (mcg/kg)	< 10	(EU) No 488/2014	na[1]	< 2	< 10	ICP-MS (ANA-130)
Arsenic (total) (mcg/kg)	< 100	FDA action level infant rice cereal	na[1]	< 30	< 100	ICP-MS (ANA-130)
Chromium (total) (mg/kg)	< 2	Manufacturer's standard	na[1]	< 0.05	< 2	ICP-MS (ANA-130)
Mercury (mg/kg)	<0.01	Manufacturer's standard (EU 2018/73 for milk)	na[1]	<0.001	<0.01	ICP-MS (ANA-130)
Others						

Aflatoxin M_1 (mcg/kg)	< 0.15	Codex Standard 193-1995	na[1]	< 0.15	< 0.15	NEN-EN-ISO 14501
Nitrate (mg/kg)	< 100	GB 2762-2017 / Dutch 'warenwetbesluit Zuivel'	na[1]	<10	< 50	ISO 14673-2
Nitrite (mg/kg)	< 2.0	GB 2762-2017 / Dutch 'warenwetbesluit Zuivel'	na[1]	< 0.2	< 2.0	ISO 14673-2
Melamine (mg/kg)	< 1	(EU) No 1881/2006	na[1]	< 0.5	< 1	ISO/TS15495 (IDF/RM 230:2010)
Dioxins and Furans WHO (2005)-PCDD/F TEQ (upper bound) (pg TEQ/g fat)	<1.75	Recommendation 2013/711/EU	na[1]	< 0.5	< 1.75	GLS DF 110 / 1613B/1668 Mod

[1] not applicable

[2] Scorched particles can be formed during drying of milk powders; particles that have been in the dryer for too long can get scorched. This is inevitable but is prevented as much as possible (see 21 CFR 131).

Table 2 shows the microbial standards for the DWGM.

***Table 2**. Microbiological Specification of the Dry Whole Goat Milk.*

Parameter	n	c	m	M	Method
Total plate count 30°C (cfu/g)	5	2	5,000	10,000	ISO 4833
Yeast and molds (cfu/g)	5	2	50	100	ISO 7954
Coliforms	5	2	10	100	ISO 4831
Coag pos Staphylococci (/g)	5	0	negative		ISO 6888-3
B. cereus spores (cfu/g)	5	2	50	100	ISO 7932
Salmonella (/25g)	15	0	negative		ISO 6579
Cronobacter (/100g)	3	0	negative		ISO 22964
L. monocytogenes (/25g)	1	0	negative		ISO 11290-1
Sulfite red. Clostridia spores (cfu/g)	5	2	30	50	VDLUFA M 7.18.4

n: Number of samples representing the batch
c: Maximum number of results between m and M
m: A count which separates good quality from marginal quality and which most test samples should not exceed
M: A count which if exceeded by any of the test samples would lead to rejection of the lot

In Table 3, the analyses of three non-consecutive lots of DWGM are compared to the specifications of the product. In addition, relevant non-specified minerals and regulated contaminants and pesticides are shown.

***Table 3**. Analysis Summary of Three Non-Consecutive Lots Dry Whole Goat Milk.*

Parameter	Specification	Lot 1	Lot 2	Lot 3	Method
Milkfat (% w/w)	Min 26% Max 40%	28.7	28.6	32.5	ISO 1736 (IDF 9:2008)
Moisture (% w/w in milk solids non-fat)	≤ 5 %	3.0	2.8	2.6	ISO 5537 (IDF 26:2004)
Milk protein (% m/m in milk solids not-fat, N*6.38)	≥ 34 %	36.0	38.6	37.6	ISO 8968-1:2014 (IDF20-1:2014)
Lactose (% w/w)		35.5	33.6	32.5	ANA-257
Chloride (mg/100g)		1359	1317	1229	ANA-306
Calcium (mg/100g)		836	854	833	ANA-131
Phosphorous (mg/100g)		795	910	828	ANA-131
Potassium (mg/100g)		1606	1638	1527	ANA-131
Magnesium (mg/100g)		101	116	100	ANA-131
Manganese (mcg/100g)		32	45	38	ANA-131
Sodium (mg/100g)		270	298	267	ANA-131
Titratable acidity (ml 0.1N NaOH/10g solids-not-fat)	≤ 18 %	11	10	9	ISO 6091 (IDF 86:2010)
Scorched particles	Max Disc B	A	A	A	ISO 5739 (IDF 107:2003)
Solubility index (ml)	Max 1	0.1	0.1	0.1	ISO 8156
Total plate count 30°C (cfu/g)	Table 2	<100	<300	<100	ISO 4833
Yeast and molds (cfu/g)	Table 2	<10	<10	<10	ISO 7954
Coliforms (cfu/g)	Table 2	<10	<10	<10	ISO 4831
Coag pos Staphylococci (/g)	Table 2	<10	<10	<10	ISO 6888-3
B. cereus spores (cfu/g)	Table 2	<10	<10	<10	ISO 7932
Salmonella (/375g)	Table 2	negative	negative	negative	ISO 6579
L. monocytogenes (/25g)	Table 2	negative	negative	negative	ISO 11290-1
Sulfite red. Clostridia spores (cfu/g)	Table 2	<10	<10	<10	VDLUFA M 7.18.4
Antibiotics	Negative	Negative	Negative	negative	Charm MRL
Lead (mg/kg)	< 0.15	< 0.02	< 0.02	< 0.02	ICP-MS (ANA-130)
Cadmium (mcg/kg)	< 10	< 2	< 2	< 2	ICP-MS (ANA-130)
Arsenic (mcg/kg)	< 100	< 30	< 30	< 30	ICP-MS (ANA-130)
Mercury (mcg/kg)	< 10	< 1	< 1	< 1	ICP-MS (ANA-130)
Aflatoxin M1 (mcg/kg)	< 0.15	< 0.1	< 0.1	< 0.1	NEN-EN-ISO 14501
Nitrate (mg/kg)	< 100	6.4	4.9	5.3	ISO 14673-2
Nitrite (mg/kg)	< 2.0	< 0.2	< 0.2	< 0.2	ISO 14673-2
Melamine (mg/kg)	< 1	< 0.1	< 0.1	< 0.1	ISO/TS15495 (IDF/RM 230:2010)
Dioxins and Furans WHO PCDD/F PCB TEQ (upper bound) (pg TEQ/g fat)	< 1.75	0.44	0.35	0.37	Conform EU 644/2017

Dieldrin + Aldrin (mg/kg fat)		< 0.02	< 0.02	< 0.02	ANA-206
DDT (sum) (mg/kg fat)		< 0.04	< 0.04	< 0.04	ANA-206
non dioxin like-PCBs (sum) (mcg/kg fat)		< 12.0	< 12.0	< 12.0	ANA-206

The method of analyses used for the parameters indicated in Tables 1, 2, and 3 are standard methods validated for the milk powder matrix. The goat milk, which is the ingredient for the above described DWGM, is monitored (twice per year) to ensure that potential contaminants of concern, including heavy metals (e.g., lead, arsenic, cadmium, mercury), aflatoxin B1, PCB (polychlorinated biphenyls) compounds, dioxins, pesticides (dieldrin, Aldrin, DDT) and veterinary drugs meet EU specifications and ensure that all milk and milk-derived products are food-grade.

2.D. Stability

DWGM is stable for at least 1 year when stored under cool and dry conditions. No significant degradation in the quality occurs up to 1 year when stored at temperatures between 10-30°C and relative humidity <70% (Table 4). The parameters as defined in the specifications in Table 1 do not change significantly during shelf life. In Table 4 the stability of DWGM is indicated for microbial parameters. In addition, organoleptic properties also stay well within acceptable ranges during a shelf life of minimally 1 year.

		Lot A	Lot B		Lot C		Lot D		Lot E		Lot F		Lot G	
	Shelf life (months) / Method	0	0	6	0	9	0	12	0	15	0	15	0	15
Sensory	Internal method[1]	5	5	5	5	5	5	5	5	5	5	5	5	5
Total plate count (cfu/g)	ISO 4833	<100	1200	1000	<100	<100	<100	<100	200	<100	200	<100	<100	<100
Yeasts & molds (cfu/g)	ISO 7954	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Moisture (%)	ISO 5537 (IDF 26:2004)	1.4	2.3	2.2	2.1	2.2	2.4	2.6	2.1	2.1	2.1	2.3	2.9	2.6

Table 4. *Stability of Dry Whole Goat Milk over 15 Months.*

[1] Scoring low to high from 1 to 5; with 5 being white to yellowish powder, milky, slightly sweet, and free from off-odor and –taste.

2.E. Intended Technical Effects

DWGM will be used as an ingredient in non-exempt term infant formula as the source of protein. It also provides lactose, fat, and some micronutrients. It is not intended to serve any function other than nutrition.

PART 3. Exposure Estimates

3.A. Intended Levels of Use of Dry Whole Goat Milk in Non-Exempt Infant Formula

21 CFR 107.100 provides nutrient specifications for milk-based infant formula per 100 kcal formula as prepared. The protein content should be at a level not less than 1.8 g and not more than 4.5 g per 100 kilocalories of the infant formula in the form prepared for consumption as directed on the container.

If DWGM is used as the sole source of protein, the minimum protein concentration in a formula of 1.8 g/100kcal would need 35 g DWGM[1]/100g formula. Although no commercial formula contains the maximum protein concentration (4.5 g/100 kcal), such would result in 88 g DWGM/100g formula. That level of DWGM would create a formula with other nutrients out of compliance. The common protein concentration in an infant formula of 2.1 g protein/100 kcal, would typically need 42 g DWGM per 100 g powdered infant formula.

The formula would have a hydration rate of 13 g powder per 100 mL formula ready to consume; this level is equivalent to 5.5 g DWGM/100 mL formula ready to consume (42% DWGM in 13 g powdered infant formula = 5.5 g DWGM/100ml formula ready to consume).

3.B. Estimated Dietary Intakes under the Intended Use

Butte[1] estimated the energy requirements of infants from total energy expenditure and energy deposition during growth. Her results showed that total energy requirements increase as expected with age and are higher in boys than in girls due to differences in weight. Per kg of body weight (bw), the highest energy requirements are at 1 month of age; 473 kJ kg^{-1} day^{-1} (113 kcal kg^{-1} day^{-1}) for boys and 447 kJ kg^{-1} day^{-1} (107 kcal kg^{-1} day^{-1}) for girls.

A goat milk-based infant formula would contain, like all non-exempt commercial infant formulas, about 65-67 kcal/100 mL when ready to consume. Therefore, to obtain 113 kcal energy kg bw^{-1}, an infant boy must consume 170 mL formula per kg bw per day. An infant girl must consume 160 mL formula per kg body weight to reach her energy consumption of 107 kcal kg^{-1} day^{-1}.

Since DWGM is to be present at a level of 5.5 g per 100 mL of prepared formula, the intake of DWGM is about 9.3 g kg^{-1} day^{-1} for boys 1 month of age (170 mL * 5.5 g/100mL) and 8.8 g kg^{-1} day^{-1} for girls (160 mL*5.5 g/100mL).

The Centers for Disease Prevention and Control (CDC) growth charts show boys' weight at 1 month of age to be 5.2 kg at the 90th percentile and girls' 4.9 kg. This means consumption of 48.4 g of DWGM per day for boys and 43.1 g of DWGM per day for girls.

Alternatively, intake data can also be calculated based on data of Stan et al. [2] who indicate for 1-month old boys an energy requirement of 480 and 517 kcal day^{-1} at the 50th and 75th percentile for bw, respectively, leading to an intake of about respectively 40 g (480 kcal / 0.66 = 727 ml *5.5 g per 100ml = 40g) and 43 g of DWGM per day.

[1] The nitrogen-to-protein conversion factor is here chosen as 6.25 as this factor deals with infant formula. When dealing with the DWGM ingredient, the standard 6.38 is chosen as the conversion factor.

Lastly, data summarized in the EFSA Scientific Opinion[3] indicate mean energy intakes of about 550-700 kcal/day for infants aged less than six months. The intake of older infants, due to their increased bw, is on the higher end and for younger infants on the lower end. An energy intake of 550 kcal per day accounts for about 46 g of DWGM (550 kcal / 0.66 = 833 ml *5.5 g per 100ml = 46g).

PART 4. Self-limiting Levels of Use

No known self-limiting levels of use are associated with DWGM. Of course, in the use of the DWGM as an ingredient in non-exempt infant formula, the final product must comply with the specifications provided in 21 CFR 107.100. Moreover, the total formula consumption of an infant is limited by its total caloric intake, based on kcal per kg bw.

PART 5. History of Consumption

The conclusion that the intended use of DWGM is GRAS is based on scientific procedures.

PART 6. Narrative

6.A. Current Regulatory Status

6.A.1. United States Current Regulatory Status of Goat Milk in Infant Formula

The FDA had no questions on a GRAS notification (GRN 644) of a combination of nonfat dry goat milk and goat whey protein concentrate (to a 60:40 whey:casein ratio) for use as the sole source of protein for non-exempt infant formulas for term infants [4]. The composition of the material in that notification did not include the fat component from goat milk. However, ingredients containing cow milk fat have been met with no questions; GRN's 980 and 1041 which describe the use of Dry Whole Milk as an ingredient in non-exempt infant formula [5,6] and the use of anhydrous milk fat in exempt infant formula in GRN 898 [7].

In 2022, FDA accepted four different infant formulae (for infants up to one year) based on DWGM in the US via the enforcement discretion in place during the formula shortage. These formulae are allowed to remain in the market during the multi-year transition period.

6.A.2. Global Regulatory Status of Goat Milk for use in Infant Formula

Many countries allow for goat milk-based infant formula based on the Codex standards for infant formula [8]. Codex defines infant formula as 'a product based on milk of cows or other animals or a mixture thereof and/or other ingredients which have been proven to be suitable for infant feeding [8].

Other regulatory agencies, in Australia and New Zealand [9], England [10], and countries in the European Union [11], have legislation and/or approvals to accept the use of protein from goats' milk in infant formula.

Of particular relevance for this GRAS determination is the 'Scientific Opinion on the suitability of goats' milk protein as a source of protein in infant formulae and in follow-on formulae' by the EFSA, published in 2012 [12]. This Opinion paved the way for infant formulas based on goat milk in the European Union. EFSA focused on the suitability of the protein, as in the EU the suitability for new protein sources in infant and follow-on formulae needs to be demonstrated through a systematic review of the available data relating to the expected benefits and to safety considerations as well as, where necessary, appropriate clinical studies, performed following generally accepted expert guidance on the design and conduct of such studies. Milk fat, either from goat milk or cow milk, is considered the obvious and previously used staple source of fat for use in infant and follow-on formulas [3].

6.B. Clinical Evidence for Goat Milk-Based Infant Formula

Clinical evidence for the safety of goat milk-based infant formula is described in five studies [13–17], adding up to a little more than 300 infants randomized to a goat milk-based infant formula. A synopsis of these studies is provided in Appendix 1.

Grant et al.[16] conducted a goat milk formula (GMF) growth rate pilot study to investigate whether feeding infant formula manufactured from full cream goat milk was nutritionally equivalent to feeding infant formula manufactured from cows' milk. Sixty-two of the 72 infants randomized (within 72 h of birth) completed the study (GMF n=30; CMF n=32). Infant weight, length, and head circumference were measured at birth and age 14, 28, 56, 84, 112, 140, and 168 days. No statistically significant difference was seen in mean weight (at study completion: 8.07 ± 0.90 kg for GMF and 7.87 ± 0.99 kg for CMF),

length, or head circumference increase between the two formula groups. The sample size requirements were estimated based on published contemporary growth studies of infants-fed milk formula. A sample size of 60, 30 in each group, was expected to provide 80% power (with α=0.05) to detect a 4 g/day difference between the GMF and CMF groups in bodyweight increase from birth to 112 days of age and a 0.08 mm/day difference between the GMF and CMF groups in body length increase during the same period. Additionally, stool frequency and consistency, sleeping and crying patterns, and adverse events were also measured. The median number of daily bowel movements was greater in the GMF group (2.4 vs 1.7, p=0.01), but there were no group differences in tolerance (bowel movement consistency, duration of crying, ease of settling) or frequency of specific adverse events (colds, coughing illnesses, ear infections, thrush, chest infections, vomiting, diarrhea, rashes, constipation, food refusal or screaming).

Han et al.[15] conducted an observational study by in-market surveillance of infants in South Korea (n=976) from birth to 12 months of age receiving either GMF, CMF, a mix of human milk and GMF, a mix of human milk and CMF or human milk alone. The infants fed human milk, GMF, or CMF during the first 4 months showed similar growth rate outcomes. The infants fed the CMF had fewer and more solid bowel movements compared to human milk-fed and GMF-fed infants. The authors concluded that GMF is suitable for infants less than 12 months of age.

The study described by Zhou et al. [13] was based on whole goat milk and vegetable fat sources and had proximate analyses as the Jovie goat milk-based infant formula (respectively 2.0 and 2.1 g protein, both have 5.3 g fat and respectively 11.0 and 10.9 g carbohydrates per 100kcal). A notable difference (apart from some smaller differences like the Jovie product is manufactured with added DHA and ARA) is that the described product in the study contained added L-tryptophan and L-isoleucine, whereas to the Jovie infant formula only L-tryptophan will be added. This difference is further discussed in 6.C.2.

Zhou et al. was a multicenter, randomized, double-blind controlled trial of a goat milk infant formula (GMF, n=101). This GMF was made from whole goat milk with added lactose, vegetable oils (canola, high oleic acid sunflower, and sunflower oils), minerals, acidity regulator (citric acid), vitamins, choline chloride, L-isoleucine, L-tryptophan, taurine, and L-carnitine. The GMF was compared to a CMF(n=99) control (demineralized whey, skimmed milk solids, whey solids, lactose, unspecified vegetable oils, soy lecithin, L-tryptophan, L-tyrosine, taurine, and acidity regulator (citric acid and/or calcium hydroxide). The growth and nutritional status of infants consuming the GMF and CMF were compared through four months of exclusive formula feeding, and up to twelve months with complementary foods included after four months. A breastfed reference group was also included (n=101).

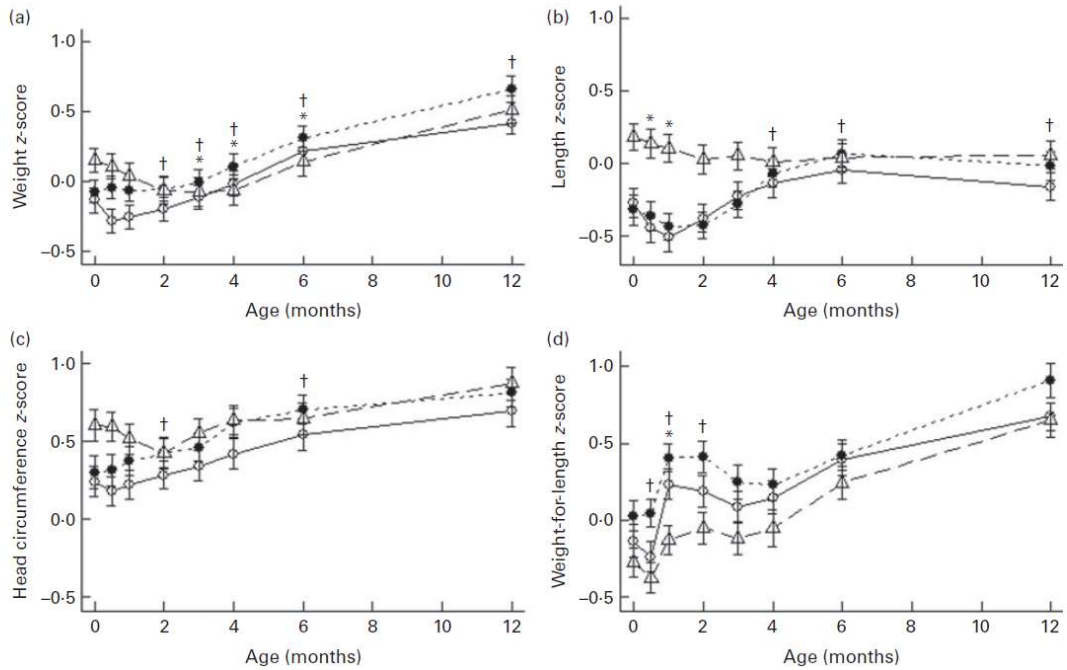

Figure 2. *Weight (a), length (b), head circumference (c), and weight-for-length (d) z-scores of infants fed goat milk formula (○), cow milk formula (●), or human milk (Δ). Z-score data were based on WHO reference data. Values are means of imputed data, with standard deviations represented by vertical bars. *Mean value of the goat formula-fed group was significantly different from that of the human milk-fed group (P<0.05). †Mean value of the cow formula-fed group was significantly different from that of the human milk-fed group (P<0.05).* Figure from Zhou et al., 2014.

The daily mean intake of the study formula was not different among formula groups through four months of age. Breastfed (BF) infants had a higher mean birth weight (BF: 3564 ± 409 g vs GMF: 3,379 ± 466 g and CMF: 3,407 ± 419 g) than those in the GMF and CMF groups. In addition, in the case of the BF infant mothers, there was a lower maternal pre-pregnancy body mass index (24.6 ± 4.5 vs 26.6 ± 6.3 vs 27.8 ± 7.6, respectively), fewer mothers who had a history of smoking during pregnancy (10 [9.9%] vs 45 [44.6%] vs 34 [34.3%], respectively), and a greater percentage of parents with a higher level of education (41% vs 6% vs 5%, respectively).

No statistically significant or clinically relevant differences in weight, length, or head circumference development between the two formula groups through four months of exclusive formula feeding were found nor at twelve months (when the infants were fed mixed diets) (Figure 2). There were small differences in linear and ponderal growth parameters between infants from the two formula groups compared to the reference breastfed infants after adjustment for the higher birth weight of breastfed infants [13].

Minor differences in blood biochemistry between the two formula groups, reflected differences in formula composition, but did not raise concern with respect to the safety and/or nutritional adequacy of the formulas according to the authors. Some statistically significant differences were observed in plasma concentrations of specific essential amino acids (EAAs) (Figure 3). Differences in the plasma levels of L-isoleucine, L-threonine, L-phenylalanine, and L-valine were reported between the formula groups, but none of the differences were considered of clinical significance by the authors. The plasma level of L-tryptophan was not different among the formula groups nor was either formula group different from the breast fed reference group.

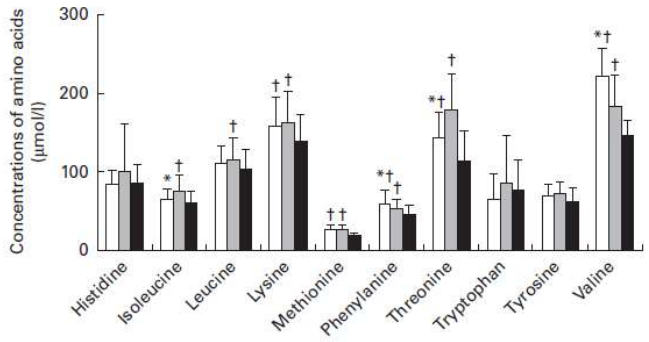

Figure 3*. Concentrations of essential and semi-essential amino acids in the plasma of infants after 4 months of being fed goat milk formula (□), cow milk formula (▒), or human milk (■). Values are means, with standard deviations represented by vertical bars. * Mean value was significantly different from that of the cow milk formula-fed group (P<0·05). † Mean value was significantly different from that of the breast milk-fed group (P<0·05).* Figure from Zhou et al., 2014.

There were no differences among formula groups in the number of stools per day, although transiently at two weeks and one month of feeding, the stool consistency in the goat milk group was softer than for the cow milk group. There were not any differences in wheezing, vomiting, loose watery stools, itchy rash, or other skin problems between the two formula groups.

Describing the above Zhou study, the EFSA Scientific Opinion[12] reported a significantly higher rate of blood-stained stools in infants randomized to goat milk infant formula (17/90, 18.8%) compared to cow's milk infant formula fed (7/86, 8%) or the breastfed (7/100, 7%) group (p<0.04). However, there were no differences in hemoglobin or ferritin levels between the two formula-fed groups, which would have indicated clinically significant blood loss. Per these authors, the clinical significance of these findings was unknown, but they noted that there was no indication of other gastrointestinal disorders, differences in stool characteristics, crying and sleeping patterns, general health, or other allergy-related symptoms. They noted that although the outcomes related to allergy and gastrointestinal function were secondary outcomes, the study did not have adequate power to rigorously assess, and thus the results need to be interpreted with caution, as it is possible that this may be due to chance or a real effect. A much larger, adequately powered randomized controlled trial with an objective assessment of clinical outcomes and biomarkers of allergy is needed to evaluate the effects of goat milk-based infant formula on allergy and gastrointestinal function. The authors concluded and EFSA acknowledged that there was no difference in the occurrence of serious adverse events leading to hospital admission or considered to be related to the type of feeding between the two formula-fed groups of infants during the twelve months [12].

A randomized controlled trial of GMF (n=31 completers) or CMF (n=34) on growth, selected blood, urine, and fecal measures of Chinese infants was reported by Xu et al. (2015)[17]. There were no differences between groups in growth over 6 months, or blood minerals, urine or fecal markers, or adverse health conditions, including respiratory illness, gastrointestinal illness, reflux, eye infection, ear, nose, and throat conditions, fever, urinary tract infection, except that there was a slightly higher blood calcium concentration among males of the GMF group at 3 months of feeding, and a higher urinary pH in the GMF group at 6 months. The proportion of infants who had any serious adverse events during the study period was similar between GMF 6/39 and CMF 7/40 groups (two diarrhea and four throat conditions in GMF; one eczema, three diarrhea, two throat conditions, and one running nose in CMF).

The study by He et al.[14] was a double-blind randomized trial comparing weight gain over 4 months of infants fed a GMF (completers per protocol, n=79) or a CMF (n=74) and included a reference group of

breastfed infants (n=65). The study was designed to address shortcomings of previous studies study on GMF; studies that were observational or underpowered or included non-exclusive feeding of the GMF, and to further investigate the reported excess incidences of blood-stained stools among infants fed GMF[13]. Infants were from 25 hospitals or pediatric practices in Germany, Croatia, Austria, and Spain. The study GMF product was based on the combination of skimmed dry goat milk and goat whey protein concentrate (2.5 g/100 kcal and the comparator had 2.0 g/100 kcal). Through 112 days of feeding, the infant formula groups showed greater mean (SD) weight z-scores than the breastfed group from 84 days onward (GMF: 0.28 (0.84), CMF: 0.12 (0.88), BF -0.19 (1.02), $p<0.05$), whereas length and head circumference z-scores were similar across all three groups.

He et al.[14] reported data for safety and tolerance measures (Table 5). Over the 16-wk intervention, the overall incidence of serious adverse events (SAE) was low for all three groups [BF (n = 4), GMF (n = 5), and CMF (n = 12)]. The risk of SAE was lower in the GMF group as compared to the CMF group, but the difference did not reach statistical significance [RR 0.39 (95% CI 0.14–1.08)] and there was no apparent difference among diet groups in the distribution of serious AEs among the three major subsets of infections and infestations, gastrointestinal disorders, and metabolism and nutrition disorders. The SAEs were considered by the authors of the study to be unlikely attributable to the type of feeding in the majority of the cases in each formula group (GMF: 80%, CMF: 83.3%).

The GMF had a significantly lower incidence of non-serious AEs as compared to the BF group [RR 0.81 (95% CI 0.67-0.98)], whereas the incidence was similar between the GMF and the CMF group [14]. The majority of the reported non-serious AEs was considered “unlikely” causally related to the intervention (GMF: 62.1 %, CMF: 73.0%). An “assured” relatedness was considered in 6.1% of the GMF and 1.6% of the CMF group. The severity of the AEs (i.e., slight, moderate, or severe) was similar between GMF and CMF.

The distribution of AEs in the three major subsets of AEs, gastro-intestinal disorders, infections and infestations, and skin and subcutaneous tissue disorders, was reported to be similar for each diet group. There was a significantly lower incidence of reflux, colic, fussiness, and flatulence among GMF-fed infants than the reference breastfed infants, but no differences were noted in these measures between GMF and CMF groups. Notably, there were no reported cases of bloody stools in any subject in this study. These investigators concluded that goat milk formula supports adequate growth, has good tolerability, and is safe for consumption by infants[14].

The detection of blood-in-stools is not uncommon in cow’s milk formula-fed infants and therefore not surprising to be found in goat milk formula-fed infants[12].

***Table 5**. Relative risk and 95% confidence interval (CI) of the adverse events (AE) and tolerability symptoms over the 16-week intervention period in the intention-to-treat analysis set (n=296) in the study of He et al.*[14].

	GMF (n = 108)	CMF (n = 102)	BF (n = 86)	GMF vs CMF	GMF vs BF
	n (%)	n (%)	n (%)	RR (95% CI)	RR (95% CI)
Safety*					
SAE	5 (4.6)	12 (11.8)	4 (4.7)	0.39 (0.14–1.08)	1.00 (0.28–3.59)
Infections and infestations	2 (1.9)	6 (5.9)	1 (1.2)		
Gastro-intestinal disorders	1 (0.9)	2 (2.0)	1 (1.2)		
Metabolism and nutrition disorders	1 (0.9)	–	–		
AE	66 (61.1)	63 (61.8)	65 (75.6)	0.99 (0.80–1.12)	0.81 (0.67–0.98)
Gastro-intestinal disorders	42 (38.9)	36 (35.3)	28 (32.6)		
Infections and infestations	32 (29.6)	33 (32.4)	42 (48.8)		
Skin and subcutaneous tissue disorders	18 (16.7)	15 (14.7)	16 (18.6)		
Tolerability symptoms					
Bloody stools	0 (0)	0 (0)	0 (0)	–	–
Reflux	86 (79.6)	87 (85.3)	68 (79.6)	0.93 (0.82–1.05)	0.81 (0.79–0.89)
Colic	82 (75.9)	84 (82.4)	83 (96.5)	0.92 (0.80–1.06)	0.79 (0.70–0.88)
Fussiness	85 (78.7)	86 (84.3)	85 (98.8)	0.94 (0.82–1.06)	0.80 (0.72–0.88)
Flatulence	84 (77.8)	86 (84.3)	84 (97.7)	0.92 (0.81–1.05)	0.79 (0.72–0.86)

BF = breast-fed; CMF = cow milk based infant formula; GMF = goat milk based infant formula. *Multiple responses possible.

The authors[14] concluded that GMF supports adequate growth, has good tolerability, and is safe for consumption by infants. Their study GMF product included skimmed dry goat milk and goat whey protein concentrate, as described in GRN644. The study product was compared with a CMF and a breastfeeding group; weight gain and z-scores for anthropometric measurements were similar after 112 days of intervention. Both infant formula groups showed greater mean (SD) weight z-scores than the breastfed group from 84 days onwards (GMF: 0.28 (0.84), CMF: 0.12 (0.88), BF -0.19 (1.02), $p<0.05$), whereas length and head circumference z-scores were similar. Incidences of serious adverse events and parent-reported reflux, fussiness, colic, and flatulence were similar among the three groups. Although their goat milk-based infant formula was based on a combination of non-fat dry goat milk with goat whey protein concentrate and vegetable fat, these data are relevant to the goat milk protein which is the subject of this GRAS document. These data confirm and add to previous data that no serious adverse events are described when goat milk protein is used in infant formula.

The clinical literature on healthy term infants fed GMF reviewed here is the same as that reviewed in GRN 644, for which the FDA had no further questions, plus the addition of two papers: Xu et al. 2015 [17] and He et al., 2022[14]. Like the previous studies, neither of these more recent studies found a difference in growth or safety measures between infants fed CMF and those fed GMF. Notably, He et al.[14], specifically examined the incidence of blood in the stools because of the report by Zhou et al.[13], and found none. Nor was blood in stools reported in any of the other clinical studies, suggesting the finding by Zhou et al. may have occurred by chance. Overall, goat milk protein-based formula has been shown to provide growth and nutritional outcomes in infants that did not differ from those provided by a standard whey-based CMF.

6.C. Protein in Infant Formula

6.C.1. Compositional Standards for Protein and Amino Acids in Infant Formulas

The purpose of the Infant Formula Act of 1980 is to ensure the safety and nutrition of infant formulas, including minimum and maximum levels of specified nutrients. 21 CFR 107.100 outlines these nutrient

specifications, including a requirement for 1.8 (minimum) to 4.5 (maximum) grams of protein per 100 kcal of infant formula.

Additionally, the biological quality of the protein in the finished product when fed as a sole source of nutrition must be verified using an appropriate modification of the Protein Efficiency Ratio (PER) rat bioassay (21 CFR 106.96(f)) or an alternative method (21 CFR 106.96(g)(3)).

The Codex[8] outlines an amino acid profile for infant formula based on human milk. Table 6 presents a summary of the Codex Standard for essential and semi-essential amino acids, in mg per g of protein compared to literature values for goat milk amino acids, and from Jovie analyses of their whole goat milk powder. Methionine and cysteine can be added together as the sulfur-containing amino acids (SAA), methionine being the essential and cysteine the semi-essential amino acid. The aromatic amino acids (AAA) tyrosine and phenylalanine can also be added together for calculation purposes. What is notable is that goat milk protein provides very similar concentrations of essential amino acids as human milk. Virtually identical values are seen in both cases for threonine, isoleucine, leucine, tyrosine, phenylalanine, and the sum of cysteine plus methionine. Goat milk provides somewhat more valine and lysine than human milk, and somewhat less tryptophan than human milk.

Table 6. *Amino acids in mg per g protein in whole goat milk compared to Codex human milk reference values*

Amino acid	Goat milk Literature values [a]	Jovie DWGM production data[b]	Codex Human Milk[c]
Histidine	28 ± 3.8	26 ± 0.5	23 ± 7.8
Threonine	47 ± 4.9	49 ± 1.5	43 ± 6.3
Valine	67 ± 4.9	68 ± 2.0	50 ± 7.0
Isoleucine	49 ± 5.0	49 ± 1.4	51 ± 5.1
Leucine	93 ± 3.7	93 ± 1.0	94 ± 9.9
Tyrosine	41 ± 6.1	38 ± 1.4	42 ± 9.3
Phenylalanine	47 ± 3.0	46 ± 0.5	45 ± 16.1
Lysine	86 ± 9.5	78 ± 0.8	63 ± 8.3
Cysteine	10 ± 1.9	10 ± 1.5	21 ± 4.7
Methionine	23 ± 2.2	24 ± 1.5	14 ± 1.4
Tryptophan	13 ± 2.1	13 ± 1.1	18 ± 5.2

[a] from Ceballos, L.S., et al. "Composition of goat and cow milk produced under similar conditions and analyzed by identical methodology." *Journal of food Composition and Analysis* 22.4 (2009): 322-329; Rutherfurd, S. M., et al. True ileal amino acid digestibility of goat and cow milk infant formulas. *Journal of dairy science* 89.7 (2006): 2408-2413; Rutherfurd, S. M., et al. "Amino acid composition determined using multiple hydrolysis times for three goat milk formulations." *International Journal of Food Sciences and Nutrition* 59.7-8 (2008): 679-690; Sawaya, W. N., et al. "Chemical composition and nutritive value of goat milk." *Journal of Dairy Science* 67.8 (1984): 1655-1659; USDA Handbook. Composition of Food, 1976. These reports convert from g N to g protein using 6.38 customary for non-human milk commodities, so values are systematically higher by 2% than the values for human milk, which use the conversion factor of 6.25.

[b] from 10 batches of D(W)GM, from April 2018 to June 2021 using milk from Austria (n=4), Netherlands (n=2) and one each from Canada, the US, France, and Germany.

[c] mean reported in Annex 1 of Codex Standard 72-1981 as revised 2006, which is based on 8 reports on milk from 21 days to 6 months of lactation; SD calculated from tabular data reported in Annex 1, converted mg/g N to mg/g protein using 6.25 g protein/g N.

6.C.2. Suitability of Dry Whole Goat Milk Powder as a Source of Protein in Infant Formula

All infant formulas must contain protein, which provides essential and semi-essential amino acids for normal growth, development, and maintenance of health in infants. The most commonly consumed infant formulas are cow milk which provides protein, with added carbohydrates (e.g., lactose), vegetable oils, and vitamins and minerals. As mentioned previously, the FDA has stated to have no further questions at this time regarding the conclusion that modified goat milk, a mixture of nonfat dry goat milk and goat whey protein concentrate, is GRAS (GRN644) for use as the source of protein in non-exempt infant formulas for term infants, provided that the ingredient statement of food products that contain the combination of both identify the source of protein.

Increasing the total content of goat milk protein is an efficient way to raise the level of the amino acids that are low relative to the pattern in human milk. Zhou et al.[13] used a total protein content of 2.0 g of goat milk protein/100 kcal, which raised the level of each essential amino acid except tryptophan above the human milk level (Table 6). They supplemented the formula with tryptophan, the limiting amino acid so that its concentration in the formula is above that of human milk. Zhou et al.[13] also supplemented the formula with isoleucine, the second most limiting essential amino acid; at 2.0 g protein/100kcal, the isoleucine level was already above the human milk level, so this addition may have been made to assure that the isoleucine level would be adequate even when manufacturing variability was taken into account.

Infants fed the GMF studied by Zhou et al[13] had plasma essential amino acid concentrations that were generally similar to those of CMF and human milk fed infants. Where there were significant differences between formula groups, the GMF group had values closer to the reference for Ile and Thr; where the CMF group was closer to the reference values for Phe and Val (Figure 3). Plasma concentration of His, Try, and notably Trp did not differ among these 3 groups of infants.

The GMF group had lower mean serum urea, creatinine, and folate concentrations compared with those in the CMF groups. The folate result is not surprising given that the CMF was formulated with 21 mcg folate /100 kcal, whereas the GMF was formulated with only 12 mcg/100 kcal. Both CMF and GMF exceed the regulatory minimum of 4 mcg/100 kcal. Serum folic acid in the GMF group was lower than that of the human milk group even though human milk folate was measured at only 5 mcg /100 kcal (as total folate, compared to the folic acid source in formulas); the mean serum folate in each diet group was reported as in the normal range[13].

Protein Efficiency Ratio (PER) studies with goat milk protein are also described in the literature. A PER study in rats performed with skimmed goat milk and goat milk butterfat gave a PER value (2.6) identical to a comparable formula based on skimmed cow milk and cow milk butterfat (2.6). Nitrogen digestibility of goat milk protein was 95%, and nitrogen retention per nitrogen intake was higher for goat milk than cow milk ($p < 0.01$) leading the authors to conclude that the nutritional value of goat milk protein is higher than that of cow milk[12]. El-zeini et al.[18] compared GMF and CMF with α-lactalbumin added to

each. The PER of the α-lactalbumin supplemented GMF (2.80 ± 0.23) was not significantly different than that of the casein control (2.60 ± 0.29) or that of the α-lactalbumin supplemented cow milk formula (2.79 ± 0.20). Neither PER study, however, used procedures specified in the AOAC method.

A PER study on DWGM-based infant formula was conducted at Product Safety Labs, Dayton (NJ), a laboratory with extensive experience running the bioassay. A goat milk-based infant formula with 10.8 g protein per 100 g formula, which was supplemented with 213 mg L-tryptophan per 100 g formula to fulfill the tryptophan level in human milk, was studied. The test diet was formulated with appropriate modifications of the AOAC International (Association of Official Agricultural Chemists, International) method for the PER test to minimize the addition of nutrients other than those necessary to ensure the diet meets the minimum nutritional requirements of the rat (except for protein). The modified control diet was nutritionally comparable to the test diet (both 10% protein by wt., carbohydrate sources, total fat and fat sources, and total crude fiber along with all vitamins and minerals) with the only notable difference being the source of protein (Unpublished).

The adjusted PER values for the test diet and the modified casein control diet were, respectively, 2.6 and 2.5 (Table 7); the adjusted PER of the test diet was 104% of the modified casein control.

Table 7*. Total individual body weight gain and diet consumption of Sprague-Dawley male albino rats fed either the test diet (n=10) or the modified casein control diet (n=10) over a 4-week test period (internal Jovie USA results, not published).*

Group No.	Mean Body Weight (g)			Diet Consumption (g)	Protein in Diet (%)	Mean Protein Consumption (g)	Mean Exp. PER	Adjusted PER
	Initial	Final	Gain					
Test Diet	57.5 ± 2.7	113.4 ± 8.2	56.0 ± 8.0	201.8 ± 21.1	9.85	19.87	2.81 ± 0.21	2.61
Modified casein control	57.5 ± 2.7	112.3 ± 6.5	54.8 ± 5.5	198.7 ± 11.9	10.23	20.33	2.69 ± 0.18	2.50

An error was discovered post-study in the compiling of the modified casein control diet that resulted in some minerals not meeting target values. Copper, selenium, zinc, iron, and iodine had final concentrations in the control diet less than intended. For copper, selenium, and iron the deviations resulted in levels that were below the National Research Council (NRC) recommendations although above levels that cause deficiency[19]. The zinc and iodine levels were below target but met NRC recommendations. Molybdenum and manganese met the NRC requirements and while over target, were not at levels that adversely affect growth[19]. The PER value in modified casein control diets in 48 similarly designed infant formula studies undertaken over the course of years averaged 2.53 (+/- 0.37), with a median value of 2.58 (data from Product Safety Labs, Dayton). The PER value for the modified casein control diet in this study is similar to the historic laboratory average casein control PER value. Also in the expert opinion of Product Safety Labs none of the deviations from targeted mineral levels in the modified casein control diet would affect rat growth.

Other measures of protein quality

Rutherfurd et al.[20] describe whole goat milk as an alternative to cow milk for the production of infant formulas and studied the true ileal amino acid (AA) digestibility of a GMF compared with a premium CMF. The 3-wk-old piglet was used as a model for the 3-mo-old infant. The formulas were fed to the piglets over a 2-wk period beginning at 1 wk of age. Digesta from the terminal ileum were collected post euthanasia and analyzed for AA content, along with samples of the formulas. True AA digestibility was determined after correcting for endogenous AA loss at the terminal ileum of pigs fed an enzyme-hydrolyzed casein-based diet, followed by ultrafiltration (5,000 Da) of the digesta. Total urine and feces collection was performed to determine the nitrogen retention from the diets. The true ileal amino acid digestibility for both formulas was high, with mean digestibilities of 93 and 96% for the goat milk formula and the cow milk formula, respectively. The investigators indicated this is consistent with high-quality milk protein products. This is also consistent with the historical data on PER studies and more recent digestibility studies as part of PDCAAS (Protein Digestibility Corrected Amino Acid Score). The true ileal AA digestibility was similar between the goat and cow milk infant formulas for all amino acids except glycine (Gly) and tryptophan (Trp), which were, respectively, 27 and 4% higher in the cow milk formula. There was no significant difference in the nitrogen retention of piglets fed the two different formulas. The authors concluded that the investigated goat milk infant formula and the cow milk infant formula were similar in terms of protein quality and digestibility.

In a related article[21], the investigators described the mineral retention in the 3-wk-old piglet. The goat milk infant formula provided a pattern of mineral retention in the 3-wk-old piglet very similar to that of the adapted cow milk infant formula. In 2008, the same authors[22] showed that whole goat milk-based infant formula has amino acids in amounts similar to human milk reference values on a per-energy basis.

Maathuis et al.[23] described the kinetics of true ileal protein digestion and the Digestible Indispensable Amino Acid Score (DIAAS) of a GMF with an adjusted whey to casein ratio (60:40), a commercial CMF and human milk. In an *in vitro* dynamic model simulating infant digestion it was found that the true ileal protein digestibility of goat and cow milk infant formula was similar to that of HM. Importantly, the 4-hr true ileal protein digestibility, expressed as a percentage of N intake, showed no significant differences among the three test products: GMF 78.3%±3.7%, CMF 73.4%±2.7%, and HM 77.9%±4.1%. The protein digestion of CMF was delayed compared to the GMF and human milk and the DIAAS of goat and cow milk infant formula was not different compared to human milk after four hours.

Similarly, Hodgkinson et al.[24] carried out DIAAS on whole goat milk-based infant formula. Under simulated gastric conditions, it was found that digestion of higher molecular weight whey proteins increased as pH decreased. β-lactoglobulin was poorly digested under all gastric digestion conditions. Caseins reacted to pH changes differently compared to whey proteins with less digestion of casein at pH 3.0 than at pH 5.0. The resulting peptide profiles suggested that casein from goat milk tended to be more efficiently digested compared to caseins from cow milk and the peptide profiles from goat milk were distinct from cow milk. This study highlights that the casein fraction behaves differently to the whey proteins under different digestion conditions; much less casein was digested at pH 3.0 than at pH 5.0, whereas there was more digestion of whey proteins at pH 3.0 compared to pH 5.0.

Follow-up research by He et al.[25] focused on identifying the differences in the physicochemical behavior of the gastric protein digestion of GMF, CMF, and HM under simulated infant digestion conditions. GMF

and CMF were, in general, similar concerning physicochemical behavior and protein breakdown properties during *in vitro* gastric digestion. However, several notable differences that may help to explain the previous observations that initial protein digestion is faster in the GMF than in the CMF and the overall protein digestion kinetics of GMF is more comparable to HM than that of CMF [23]. While HM formed larger aggregates than either CMF or GMF, GMF coagulated to slightly larger, less compact aggregates than those of CMF as shown under the stereomicroscope and it showed higher turbidity than CMF.

Gastric emptying is a major factor controlling the kinetics of milk nitrogen absorption, as milk proteins are rapidly absorbed after they reach the small intestine. The protein content in the serum phase of the GMF was lower than that of HM but tended to be higher than that of the CMF, which may explain, at least partly, the faster initial digestion of HM and GMF. Physicochemical changes upon gastric digestion of protein, including separation into a cream and serum phase, the disappearance of the close-knit network under a stereomicroscope, decreases in particle size, and a slight increase in viscosity (lower than CMF), were observed at an earlier stage of digestion, i.e., at higher pH, in GMF than in CMF. This might be correlated to a faster initial digestion as reported by Maathuis et al.[23]. However, protein digestion in the stomach in young infants is likely limited, due to a low level of pepsin and high gastric juice pH (about pH 8 directly following birth → decreases to ~ 2-4 as stomach begins to secrete acid) which is not optimal (pH 1.2 to 2.5) for pepsin activities.

These various methods of establishing the quality of whole goat milk protein are not safety outcomes for use of dry goat milk as an ingredient in infant formula, but they demonstrate that when used as an ingredient in infant formula, DWGM satisfies the quality requirement for infant formula protein.

6.D. Fat in Infant Formula

6.D.1. Compositional Standards for the Fat Fraction in Infant Formulas

The amount of fat in infant formula is specified in 21 CFR 107.100, which also includes a requirement for percent of calories (30 % minimum to 54 % maximum) from fat. In addition, it is specified that linoleic acid will be present at a minimum of 300 mg per 100 kcal of the infant formula.

The Life Sciences Research Office (LSRO) Expert Panel[26] recommended that infant formulas for term infants provide 4.4 to 6.4 g fat per 100 kcal, 8 to 35% of total fatty acids as linoleic acid, 1.75 to 4.0% of total fatty acids as α-linolenic acid, and a ratio of linoleic acid to α-linolenic acid of at least 6:1 and not more than 16:1. The recommendation to include specifications for α-linolenic acid resulted from evidence indicating that α-linolenic acid is a precursor for the formation of n-3 long chain polyunsaturated fatty acids, including docosahexaenoic acid (DHA). In current formulas, where DHA and ARA are supplemented to significant levels, a lower minimum content for alpha-lipoic acid (ALA) was proposed (0.05 mg/100 kcal) by EFSA, whereas LSRO proposed 0.1 mg/100 kcal for infant formula not supplemented with ARA and DHA[3]. Infant formulas marketed in the United States need not contain DHA or ARA; however, most of these kinds of products contain both of these long-chain fatty acids deemed critical for neurodevelopment.

6.D.2. Suitability of Dry Whole Goat Milk Powder as a Source of Fat in Infant Formula

Fat is an important component of human milk and infant formula, providing about half of the daily energy requirement.

As discussed in section 3.A., typically 42 g DWGM will be used per 100 g Infant Formula. As DWGM contains about 29% fat, the DWGM will deliver about 12.2 g fat per 100 g of formula, whereas around 26.5 g fat is necessary for the 21 CFR 107.100 specified amount of fat in Infant Formula. Hence, milk fat will be supplemented with vegetable oils to reach the required total fat. These vegetable fats also supplement the amount of linoleic acid to the required level and increase α-linolenic acid. Clinical trials described in the literature regarding the suitability of goat milk protein in infant formula have also used infant formula based on whole goat milk supplemented with vegetable oils. The study by Zhou et al.[13] was performed with a goat milk-based infant formula with about 60% milk fat and was found to provide growth that did not clinically differ from growth provided by a standard whey-based cow milk formula with added vegetable oils.

The average fatty acid composition in goat milk, cow milk, and human milk fat is depicted in Table 8 (taken from Gallier et al.[27]).

***Table 8**. Average Fatty Acid Composition in Goat Milk, Cow Milk, and Human Milk Fat (from Gallier et al., 2020[27])*

	Human Milk [1] Europe	Human Milk [1] Asia	Cow Milk [2]	Goat Milk [2]	Whole Goat Milk-Based IF [3] 48% MF	Whole Goat Milk-Based IF [4] 55% MF	Cow Milk-Based IF Vegetable Oil Only [6]	Cow Milk-Based IF MF [1]
Butyric acid C4:0	ND	ND	3.2–3.3	2.0–2.6	1.17	3.1	ND	2.4
Caproic acid C6:0	0.39	0.07	1.6–2.1	2.4–2.9	1.06	2.5	ND/0.2	1.3
Caprylic acid C8:0	0.19 (0.09–0.24)	0.17 (0.11–0.28)	1.2–1.3	2.7–2.7	1.11	2.0	1.2/2.5	1.7
Capric acid C10:0	1.29 (0.83–1.63)	1.31 (0.52–2.48)	3.0–3.1	8.4–9.7	3.43	7.3	1.1/1.8	2.2
Lauric acid C12:0	5.98 (4.15–8.33)	5.56 (2.97–13.82)	3.1–3.3	3.3–4.3	1.54	4.2	5.4/13.4	6.3
Myristic acid C14:0	6.44 (4.98–9.38)	5.70 (3.50–12.12)	9.5–12.1	9.6–10.3	3.68	7.0	4.6/5.2	7.2
Myristoleic acid C14:1	0.18	0.26 (0.03–1.11)	0.7–1.1	0.09–0.16	0.12	ND	ND/ND	0.8
Pentadecanoic acid C15:0	0.25 (0.16–0.32)	0.20 (0.08–0.50)	ND	ND	0.35	0.6	ND/ND	0.6
Palmitic acid C16:0	21.93 (15.43–25.62)	21.78 (17.55–29.00)	26.5–32.2	24.6–27.7	12.30	17.0	26.3/7.7	18.9
Palmitoleic acid C16:1 *n-7*	1.98 (1.65–2.31)	2.44 (1.29–4.59)	ND	ND	0.39	ND	0.6/0.1	1.1
Heptadecanoic acid C17:0	0.29 (0.22–0.33)	0.28 (0.19–0.41)	ND	ND	0.29	0.4	ND/ND	0.3
Stearic acid C18:0	7.37 (5.58–9.52)	5.58 (3.90–6.79)	8.9–14.6	9.7–12.5	5.89	6.3	5.3/3.2	6.7
Oleic acid C18:1 *n-9*	36.30 (28.93–41.69)	30.80 (21.85–36.96)	19.3–24.1	19.4–24.0	40.65	31.0	37.6/43.3	28.1
Linoleic acid C18:2 *n-6*	13.99 (10.16–16.59)	16.90 (7.53–24.29)	ND	ND	10.79	14.0	14.0/20.5	16.7
Conjugated linoleic acid C18:2 *c9, t11*	0.27–0.49 [5]	ND	0.1–1.9	0.4–3.7	0.33	ND	ND/ND	ND
α-linolenic acid C18:3 *n-3*	0.76 (0.49–1.05)	1.47 (0.35–4.06)	ND	ND	1.58	1.2	1.6/1.8	1.5
Arachidic acid C20:0	0.21 (0.14–0.31)	0.32 (0.03–2.97)	ND	ND	0.24	0.3	ND/0.3	0.3
Arachidonic acid C20:4 *n-6*	0.47 (0.37–0.64)	0.64 (0.30–2.57)	ND	ND	0.45	ND	0.3/0.3	ND
Eicosapentaenoic acid C20:5 *n-3*	0.09 (0.05–0.13)	0.31 (0.07–1.59)	ND	ND	0.12	ND	ND/0.0	ND
Behenic acid C22:0	0.09 (0.05–0.13)	0.08 (0.05–0.14)	ND	ND	0.33	ND	ND/0.4	0.1
Docosahexaenoic acid C22:6 *n-3*	0.28 (0.18–0.42)	0.55 (0.19–1.13)	ND	ND	0.44	ND	0.2/0.2	ND
Tetracosanoic acid C24:0	0.07 (0.03–0.16)	0.07 (0.01–0.14)	ND	ND	0.21	ND	ND/0.1	ND

[1] from [3]. [2] from [26]. [3] Measured using gas chromatography ($n = 2$). [4] from [25]. [5] from [29]. [6] from [3]; values (%/%) are for cow milk-based IF manufactured with a blend of vegetable oils with palm oil/without palm oil. ND: not determined. IF: infant formula. MF: milk fat.

Total fat content and the type of fatty acids are similar in goat and cow milk[28–30] , in goat milk a little higher level of medium chain fatty acids (MCFA: caprylic and capric) and branched-chain fatty acids, such as 4-methyl- and 4-ethyl-octanoic acid, is found (Table 8). These fatty acids give goat milk its characteristic flavor. Infants absorb medium-chain saturated fatty acids more readily than longer chain saturated fatty acids[31], although the clinical significance of this for healthy infants is unclear. Human milk has more oleic, DHA, ARA, linoleic acid, and ALA than goat milk[29]. Therfore, to approximate human milk fatty acid patterns, GMF should be supplemented with oils from other sources rich in these fatty acids.

The structures of tri-acylglycerides (TAGs) in fat from vegetable sources differ from those of human milk, which may impact the digestibility of specific triglycerides. TAGs with saturated long chain fatty acids (LCFA) like C16:0 or C18:0 in the sn-1 position are the main concerns. Goat milk fat contains sn-2 palmitic

acid[32] which allows the sn-2 fatty acids to more closely resemble those of human milk when compared to vegetable oils used in infant formula manufacture.

6.E. Review of Safety Data – Animal In-Vivo Studies on Goat Milk

While there are no traditional toxicology studies on DWGM, there have been several studies in animals using goat milk[33–43], goat milk protein[44], goat milk fat[45], and goat milk infant formula[21,46]. These studies focused on the comparison of (dry) whole goat milk to cow milk with regard to the nutritive value and /or bioavailability of specific minerals. None reported adverse effects of feeding goat milk protein or fat.

6.F. Allergenicity

Initially, goat milk was suggested as an alternative to be used in hypoallergenic infant formulas for cow milk allergic patients[47–49], but in recent years, there has been growing evidence that infant formulas based on intact goat milk proteins are not suitable as an alternative to hypoallergenic infant formulas for the management of cow milk allergy (CMA) due to great protein homology. Several studies have shown that cow milk allergic patients may manifest cross-reactivity towards goat milk proteins. Zhou et al[13] reported no differences in the objective assessment of allergy-related outcomes including dermatitis and medically diagnosed food allergy in their study. EFSA has concluded that not all patients with cow milk allergy can tolerate goat milk and that most react to goat milk[50–52]. In fact, Diagnosis and Rationale against Cow Milk Allergy (DRACMA) guidelines[53] as well as the 2012 opinion by the EFSA Scientific Panel [12] highlighted the importance of avoiding goat milk for CMA management[54].

Allergy to goat milk in the absence of CMA is rare[55]. In fact, allergy to goat milk in the absence of CMA, has not been described among infants younger than 1 year of age. A small study among CMA children (n=26; ages 5 mos to 7 yrs) demonstrated these children were radioallergosorbent test (RAST)-positive to goat milk[50]. Importantly, Goh et al. (2019)[56], Martins et al. (2005)[55], and Ah-Leung (2006)[57] described cases of children (ages 2 to 16 years) allergic to goat milk whereas they were cow milk tolerant[55–57]. Zhou et al[13] found no differences in the objective assessment of allergy-related outcomes including dermatitis and medically diagnosed food allergy.

6.G. Dry Whole Goat Milk and Infant Exposure to Dioxins

Because whole goat milk contributes fat to the infant formula, attention was given to the potential adverse effects of goat milk fat. The most studied contaminant in milk is dioxin and its numerous structurally-related congeners (collectively referred to here as dioxins). Dioxin levels in human milk have been used to monitor potential infant exposures. There are many uncertainties in such estimates. For example, the concentration of congeners in human milk is not uniformly related to their concentrations in serum (which is the usual biomonitoring compartment); the upper safe limits of exposure are calculated from models that used serum concentrations of total dioxins in children as the marker for adverse outcomes in their adulthood, and that exposures during infant development may have different outcomes than the outcomes in adults used to estimate tolerable intakes.

The EPA reference dose (RfD) of 0.7 pg TEQ[2]/kg/d is deemed applicable to infants [58]. RfD is the daily exposure to humans (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious effects during a lifetime[59].

The use of the RfD provides another comparative element of product safety. In this case, the TEQ values of goat milk formula allow easier comparison of dioxin and its congeners with those that may be detected using the same metric. The current data set indicates dioxins levels from goat milk-based infant formula made using DWGM at 42% of solids calculates to an exposure of 0.05 TEQ pg/g formula as shown below.

According to a WHO/UNEP global survey of PCDDs, PCDFs, PCBs, and DDTs in human milk, the dioxin TEQ in human milk was 1-2 orders of magnitude higher than the estimated safe intake across the 53 countries studied[60]. Commenting on this global report, Abraham[61] noted that there are no agreed adverse clinical effects of dioxins observed in breastfed infants and that serum dioxin levels of breastfed infants converge on the serum levels of formula-fed infants over the course of a few years because of dilution of initial levels by rapid growth, exposure from sources other than infant nutrition and possibly age-related changes in excretion.

Dioxins level in goat milk from The Netherlands is similar to cow milk from The Netherlands. Cow milk in The Netherlands was reported to have 0.5 pg TEQ/g fat[7]. Three lots of dry goat milk powder had 0.31, 0.25, and 0.26 pg TEQ/g fat using the CDC method of accounting for non-detectable levels of individual congeners. (See Appendix B for the estimated levels that use various methods to account for undetected congeners).

Dioxins level from goat milk-based infant formula made using DWGM at 42% of solids calculates to an exposure of 0.05 TEQ pg/g formula, (see Appendix B) similar to 0.04, 0.05, and 0.11 pg/g formula for cow milk formula, soy formula, and hypoallergenic infant formula samples, respectively[62]. Estimates of exposures across a range of formula compositions generate exposures comparable to those from other infant formulas, and at the RfD.

Summarizing these observations and statistics, there are three key points.

- The dioxin TEQ in human milk, although limited evidence indicates a decline of dioxins in some developed countries (Japan, Sweden, Denmark, Canada), is greater than that detected in traditional infant formulas.
- There is not any indication that the average acute or chronic exposures to the dioxins in current infant formulas and human milk contribute to adverse health effects. However, the available literature does not provide conclusive evidence of consistent or clinically relevant health consequences to infants exposed to environmental chemicals like dioxins in breast milk or in infant formulas.
- Considering the average levels of dioxins in the proposed dry goat milk powder are below the RfD, the risk from dioxins particularly in the proposed use of DWGM in infant formula is similar to traditional infant formulas and lower than human milk.

[2] TEQ is the sum of exposures of congeners, corrected for relative toxicity. Not all congeners may be at levels of detection, and various methods are used to account for incomplete data. CDC prefers to input the value of the square root of the limit of detection for congeners below the limit of detection. *CDC uses the LOD divided by sq rt 2

6.H. Discussion of Information Inconsistent with GRAS Determination

The available data and information all appear to be consistent with the conclusion of the GRAS determination.

6.I. Conclusions and Statement of the Expert Panel

We, the members of the Expert Panel, qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food, have performed a comprehensive and critical review of available information and data on the safety and Generally Recognized As Safe (GRAS) status of *Dry Whole Goat Milk* (DWGM) as an ingredient in non-exempt infant formula. DWGM has been shown to be safe and GRAS, using scientific procedures, under the Federal Food, Drug, and Cosmetic Act (FFDCA), as described under 21 CFR §170.30(b).

This GRAS determination for the use of DWGM as an ingredient in non-exempt infant formula at a maximum level of 45g DWGM per 100g powdered infant formula (up to 2.1 g protein per 100 kcal) is based upon scientific procedures as described under 21 CFR §170.30(b). The intake of DWGM from the intended uses specified above has been shown to be safe and GRAS, using scientific procedures, under the Federal Food, Drug, and Cosmetic Act (FFDCA), Section 201(s). To demonstrate that DWGM is safe, and GRAS, under the intended conditions of use, the safety of the intake of DWGM has been determined to be GRAS by demonstrating that the safety of this level of intake is generally recognized by experts qualified by both scientific training and experience to evaluate the safety of substances directly added to food, and is based on generally available and accepted information.

The proposed use of DWGM as an ingredient in non-exempt infant formula has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(b) based on the following:

- The proposed use of DWGM as an ingredient for non-exempt infant formula at an inclusion level of around 42 g/100g of powdered formula or about 55 g/L of reconstituted non-exempt infant formula has been determined to be safe through scientific procedures set forth under 21 CFR §170.30(a) and 21 CFR §170.30(b) based on criteria that are generally accepted by the scientific community to document the GRAS status. These criteria include the comparability of the nutritional composition to cow milk, decades of research on its physical properties and physiological contributions, and an EFSA critical review of and Opinion that the protein from goat milk can be suitable as a protein source for infant and follow-on formulae.

- Goat milk protein is considered to be of equivalent quality to casein controls (modified ANRC casein) as assessed via classic PER studies. These results are consistent with additional studies among piglets and *in vitro* models that indicated the digestibility of goat milk is at least comparable to that of cow milk.
- No traditional toxicology studies in laboratory animals were reported in the scientific literature. There have been 15 studies on animals using goat milk, goat milk protein, goat milk fat, and goat milk infant formula. These studies focused on the comparison of (dry) whole goat milk to cow milk with regard to the nutritive value and /or bioavailability of specific minerals. None reported adverse effects of feeding goat milk protein or fat.
- Prior to processing raw goat milk, the product is evaluated to ensure the absence of antibiotic residues in accordance with EU Maximum Residue Limits. This evaluation includes an array common beta-lactams.
- The specifications and composition of DWGM are substantially equivalent to those described in GRN 644 (Nonfat Dry Goats' Milk and Goat Whey Protein, 2016) and GRN 980 (Dry Whole Milk, 2020). These notifications evaluated the safety of the dairy sources, which received no comments letter from the FDA.
- Five separate studies among infants fed goat's milk-based infant formula, three using DWGM and two using a mixture of Dry Skimmed Goat Milk plus goat milk whey proteins, assessing growth and development indicated the typical anthropometrics (length-for-age, weigh-for-age, head circumference-for-age) did not differ between those fed the goat milk based infant formulas and controls fed cows whey-based infant formula. The goat milk infant formula was well-tolerated, and other measured outcomes, such as bowel movement frequency, vomiting (parent-reported reflux), diarrhea, constipation, and flatulence did not differ from the control group fed standard cow's milk-based infant formula.
- DWGM based infant formula is not to be marketed as an alternative to hypoallergenic infant formulas for the management of cow milk allergy, in accordance with the notification of EFSA. Cow milk allergic patients may manifest cross-reactivity towards goat milk proteins. Allergy to goat milk in the absence of cow milk allergy is rare, and has not been reported among infants younger than one year of age.

Determination of the GRAS status of DWGM under the intended conditions of use has been made through the deliberations of a panel of experts. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. These experts have carefully reviewed and evaluated the publicly available information summarized in this document, including the safety of *DWGM* and the potential human exposure to *DWGM* resulting from its intended use as an ingredient in non-exempt infant formula, and have concluded:

There is no evidence in the available information on DWGM that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when DWGM is used at levels that might reasonably be expected from the proposed applications. DWGM is GRAS for use in non-exempt infant formula as proposed by Jovie USA LLC.

Therefore, *DWGM* is GRAS at the proposed levels of use. It is, therefore, excluded from the definition of a food additive, and may be used in the U.S. without the promulgation of a food additive regulation by the FDA under 21 CFR.

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I. Appendixes

Appendix A. Characteristics of clinical trials assessing the adequacy of goats' milk as a source of protein and amino acids in infant formula

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
Grant *et al.*, 2005[16]	Single-centre, prospective, double-blind, randomized, controlled	To compare growth of infants fed goat milk infant formula or cow milk infant formula and to compare tolerability and safety of the two formulas	• New Zealand • Birth to 168 days • 77 infants registered • 72 infants randomized 62 infants in final sample	• Goat and cow milk infant formulae did not differ in the amount of protein, fat or carbohydrate. Energy density differed slightly being 290 kJ per 100 ml for goat milk formula and 274 kJ per 100 ml for cow milk formula • Feeding instructions had mothers administer 150-200 ml of	• Infant weight, length and head circumference were measured in triplicate • Study nurse visited infants at 72 hours, and at 14, 28, 56, 84, 112, 140 and 168 days of age, at which point infants were measured and study diaries were reviewed • Stooling frequency and consistency, duration of crying, and ease of settling were monitored at each visit	• The difference in average weight gain and increase in length over the study period for infants fed goat milk formula vs. cow milk formula was not significant. • Frequency of vomiting, diarrhea, constipation, and food refusal or screaming did not differ between the two groups.	• Growth of infants fed goat milk infant formula is not different to that of infants fed cow milk infant formula. • The safety and tolerability of goat milk infant formula did not appear to differ from that of cow milk infant formula. • Data from this study indicate that goat milk infant formula is a suitable alternative to cow milk infant formula in healthy, non-allergic children.

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
				formula/kg per day • Infants fed study formula from age 1-3 days until 168 days • Caregivers were permitted to introduce weaning foods after 112 days		• Average daily intake of formula did not differ significantly for infants randomized to goat milk formula (820±133 ml) compared to cow milk formula (865±125 ml). • No difference between groups in bowel motion consistency, duration of crying or ease of settling. Bowel motion frequency in the goat milk infant formula group was greater than in the cow milk infant formula group, it was not excessive and not associated with any difference in consistency.	
Han *et al., 2011*[15]	Prospective cohort (in-	To measure weight gain up	• Korea	• Goat milk infant formula contained	• Infant weights and body heights at	• The type of feeding (breast	• In this study the infants fed goat infant formula either alone or in

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
	market surveillance)	to 12 months and stool characteristics of infants fed formulas based on goat or cow milk compared with those fed breast milk only or a mixture of breast milk and formula milk from birth to 4 months of age.	• Birth to 12 months • 1,297 infants recruited • 976 infants in final sample Infants were retrospectively categorized into 5 feeding groups: 1) breast milk (n=659; 49% males); 2) goat infant formula (n=32; 63% males); 63% males) Cow infant formula (n=159; 49% males); 4) mix of breast and goat infant formula (n=40; 53% males); 5) mix of breast milk and cow infant formula (n=86, 64% males)	80:20 ratio of casein:whey and had 55% of total fat from milk, with remaining fat consisting of high oleic sunflower, sunflower, coconut, and soy oils • Infants in the breast milk, goat infant formula, or cow infant formula groups received more than 80% of all feeding from birth to 4 months as either breast milk or formula • Infants fed a mix of breast milk and either cow or goat infant formula received less than 80% of breast milk or formula. • After 4 months, the feeding mode was varied according to the mothers' discretion, including	birth and at 4, 8 and 12 months • Stool number and consistency were recorded; consistency was graded by mothers, using an analogue scale composed of runny, soft or pasty, soft but well formed, firm, and hard as the categories	milk or formula or combination of the two) had no significant influence on weight or height of infants at any time point. • Average number of stools per day did not differ significantly between groups. • Frequency of bowel movements in goat infant formula group was similar to that of infants in breast milk. • Infants in cow infant formula group were more likely to have only 1-2 bowel movements per day and less likely to have >7 bowel movements per day compared to infants in breast milk group.	combination with breast milk during first 4 months of life had comparable growth rates over 12 months and gastrointestinal function as breast milk-fed Korean infants. • There is every indication that goat infant formula, when properly formulated, is suitable for infants less than 12 months of age.

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
				introduction of solids.		• Consistency of stools in cow infant formula group tended to be more formed or firm compared to those in either the breast milk or goat infant formula group.	
Zhou *et al., 2014*[13]	Double-blind, randomized, controlled	To compare the growth and nutritional status of infants fed formulas based on either goat milk or cow milk in a well-powered randomized controlled trial. Secondary aim was to examine a range of health- and	• Australia • 1180 families recruited • 301 families randomized • 301 infants included in analysis of growth • 240 infants included in the analysis of blood biochemistry and plasma amino acids	• 3 trial arms: goat milk formula (treatment group), cow milk formula (control group), breast-fed (reference group) • Infant formula made from whole goat milk without added whey proteins (whey:casein ratio of 20:80) • Mean daily intake of study formula ranged from 698 ml in the first 2	• Infant weight, length and head circumference, at enrolment, 2 weeks, and 1,2,3,4,6 and 12 months • Non-fasting blood samples analyzed for Hb, packed cell volume, serum creatinine, urea, albumin, ferritin, folate, and plasma amino acids at 4 months as indicator of general nutritional status	• No differences in intent-to-treat analyses of weight, length, head circumference and weight-for-length z-scores between the two formula-fed groups. • Differences in weight or weight-for-length z-scores persisted for 12 months between the breast-fed infants	• The growth and blood biomarkers of nutritional status of infants fed a whole-goat milk-based infant formula did not differ from those of infants fed a standard cow infant formula with added whey. • Lack of a significant difference between the formula-fed groups for an extensive range of health-related outcomes and for the occurrence of serious adverse events supports the safety of using goat milk in infant formula.

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
		allergy-related outcomes, including incidence and severity of dermatitis		weeks to 1000 ml at 4 and 6 months • Parents/caregivers were asked to feed their infants the allocated study formula from enrolment to at least 4 months of age and thereafter with other complementary foods up to 12 months of age. Timing of introduction of solids about 4 and 6 months was at the discretion of the families.	• Stool frequency, consistency and effort as indicators of general tolerance to formula (Bristol Stool Scale) • Sleeping patterns also assessed (Sleep and Settle Questionnaire)	and cow milk formula-fed infants, but there was no differences between goat milk formula-fed infants and breast-fed infants. • Minor differences in blood biomarkers between formula-fed groups, likely due to compositional differences of the formulae; however, concentrations of these biomarkers at 4 months were within normal reference range for infants of this age. • There were some statistically significant differences in essential and semi-essential	

Reference	Design	Aim of Study	**Sample Characteristics** - Country - Age range - Gender - # recruited - # randomized - # in final sample	**Exposure and Duration** - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
						amino acids between formula-fed groups and with breast-fed infants (e.g. valine, isoleucine, , threonine, phenylalanine), but they are unlikely to be clinically important as the mean plasma amino acid concentrations in infants in both formula-fed groups were similar to those reported in other studies. • There were some differences in sleeping patterns between formula-fed and breast-fed infants, but differences were inconsistent. • No differences in risk of an adverse health	

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
						condition between the two formula-fed groups. No differences in the objective assessment of allergy-related outcomes including dermatitis and medically diagnosed food allergy. • A significantly higher rate of blood-stained stools was found in infants randomized to goat milk infant formula (17/90, 18.8%) compared to cow's milk infant formula fed (7/86, 8%) or breastfed (7/100, 7%) group ($p<0.04$).	

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
						• Stool frequency in both formula-fed groups was significantly lower than that in the breast-fed group.	
Xu *et al*., 2015[17]	Double blind randomized	To compare the growth and nutritional status of infants fed goat milk based formula and cow milk based formula	Conducted in Beijing, China. Double-blind randomized controlled trial. Total recruited 79 infants aged 0-3 months old randomized in GMF or CMF group	6 months formula feeding	• The weight, length, and head circumference were measured at the enrolment, 3 and 6 months. The start time and types of solid food were recorded. Blood elements, urinal, and fecal parameters were also tested.	• There were no differences in the adjusted intention-to-treat analyses of weight, length, head circumference, and BMI z-scores between the two formula-fed groups over the 6-month study. • Similarly, there were no remarkable differences in the timing and types of solid food, blood elements, urinal, and feces parameters, between the	GMF-provided growth and nutritional outcomes did not differ from those provided by CMF.

Reference	Design	Aim of Study	Sample Characteristics - Country - Age range - Gender - # recruited - # randomized - # in final sample	Exposure and Duration - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
						GMF and CMF group. • No group differences have been shown in bowel motion consistency, duration of crying, ease of settling, or frequency of adverse events.	
He *et al.*, 2022 [14]	Double blind randomized	To determine the growth and safety parameters in newborns fed a goat milk based infant formula using a randomized double-blind trial, in which a cow milk formula served as a control and a breast fed group as a reference.	• Conducted in 25 European study centers (Germany, Croatia, Austria and Spain). • Aged up to 14 days. • Stratified by gender. • 210 formula fed infant were randomized. • A total of 74 infants completed the study in the GMF and 79 infants in the CMF group.	112 days of infant formula or breast feeding.	• Anthropometric measurements (weight, length and head circumference) were performed in duplicate at baseline, at day 14 (visit 2), 28 (visit 3), 56 (visit 4), 84 (visit 5), and 112 (visit 6). • Stool characteristics and tolerability symptoms (i.e. reflux, colic, flatulence, and	• Comparing the GMF to the CMF group, weight gain [mean difference 227.8 g (95% CI -16.6-439.0)] and z-scores for anthropometric measurements were similar after 112 days intervention. Infant formula groups showed greater mean (SD) weight z-scores than the BF group from 84 days onwards (GMF: 0.28 (0.84),	The data demonstrate that goat milk formula provides adequate growth, has a good tolerability and is safe to use in infants.

Reference	Design	Aim of Study	**Sample Characteristics** - Country - Age range - Gender - # recruited - # randomized - # in final sample	**Exposure and Duration** - Dose / exposure; method and frequency of consumption - Duration of intervention or follow-up	Outcome Measures	Results	Conclusions
			• 65 infants per group completed the study without major protocol deviations.		fussiness), and IF consumption were reported. • Stool consistency and color were assessed. • Occurrence of AE and medical treatments were orally discussed and assessed during the study visits.	CMF: 0.12 (0.88), BF -0.19 (1.02), p	

Appendix B. Dioxins, furans, and dioxin-like polychlorinated biphenyls (PCBs)

Dioxins, furans, and dioxin-like PCBs are a group of substances with similar molecular structures and similar toxicological modes of action. The exposure assessment for dioxins and dioxin-like substances follows a specific approach in which the dioxin exposure is calculated for the mixture of PCDDs (dioxins), PCDFs (furans), and dl-PCBs (dioxin-like PCB congeners). Of this mixture, 2,3,7,8-TCDD (a PCDD) is the most toxic congener. This congener was assigned a toxic equivalency factor (TEF) of 1. Accordingly, other congeners have been assigned TEFs as a fraction of 1, according to their toxicity relative to 2,3,7,8-TCDD. In assessing total exposure to dioxin-like compounds, the concentration of each congener is multiplied by its respective TEF, and then all adjusted congener concentrations are summed. This total is referred to as the Toxicity Equivalence (TEQ).

Table B.1. *WHO-TEFs for Human Risk Assessment*[66]

Congener	TEF value	Congener	TEF value
Dibenzo-p-dioxins ('PCDDs')		**'Dioxin-like' PCBs Non-ortho PCBs + Mono-ortho PCBs**	
2,3,7,8-TCDD	1	*Non-ortho PCBs*	
1,2,3,7,8-PeCDD	1	PCB 77	0,0001
1,2,3,4,7,8-HxCDD	0,1	PCB 81	0,0003
1,2,3,6,7,8-HxCDD	0,1	PCB 126	0,1
1,2,3,7,8,9-HxCDD	0,1	PCB 169	0,03
1,2,3,4,6,7,8-HpCDD	0,01		
OCDD	0,0003	*Mono-ortho PCBs*	
Dibenzofurans ('PCDFs')		PCB 105	0,00003
2,3,7,8-TCDF	0,1	PCB 114	0,00003
1,2,3,7,8-PeCDF	0,03	PCB 118	0,00003
2,3,4,7,8-PeCDF	0,3	PCB 123	0,00003
1,2,3,4,7,8-HxCDF	0,1	PCB 156	0,00003
1,2,3,6,7,8-HxCDF	0,1	PCB 157	0,00003
1,2,3,7,8,9-HxCDF	0,1	PCB 167	0,00003
2,3,4,6,7,8-HxCDF	0,1	PCB 189	0,00003
1,2,3,4,6,7,8-HpCDF	0,01		
1,2,3,4,7,8,9-HpCDF	0,01		
OCDF	0,0003		

Abbreviations used: 'T' = tetra; 'Pe' = penta; 'Hx' = hexa; 'Hp' = hepta; 'O' = octa; 'CDD' = chlorodibenzodioxin; 'CDF' = chlorodibenzofuran; 'CB' = chlorobiphenyl. ◄

When the analysis of any congener results in a measurement below its limit of quantitation (LOQ), a value is generally assigned to that measurement. There are numerous approaches to assigning a value to provide a numerical value for measurements below the LOQ. The approach selected can have a substantial effect on the value for overall TEQ, as it is often the case that many of the congeners in a

sample (e.g., of milk, serum) may be below the LOQ. The most conservative assumption (Upper Bound) is to assign measurements below the limit of quantification a value equal to the LOQ. This is the most conservative approach from a safety standpoint because it generates the highest TEQ value. The least conservative approach (Lower Bound) is to assign a value of zero for each congener that is below the LOQ. Another approach used by the US Centers for Disease Control and Prevention (for example, for NHANES) and by many researchers is to assign a value of the LOQ divided by the square root of two (NHANES 2003-2004 Data Release January 2006 General Information about the NHANES 2003-2004 Laboratory Methodology and Public Data Files).

Dioxins in cow milk, goat milk, human milk, and infant formula

The European food grade specification for dioxins in milk and dairy products is TEQ <4.0 pg/g fat (EC no 2022/2002). In The Netherlands, the median value for the Upper Bound total dioxins in cow milk including the dl-PCBs was 0.53 in the years 2012-2016, and the maximum value in the 2016 sample was 0.58 pg TEQ/g fat[7]. Dioxins levels in cow milk sampled in 2017 in The Netherlands had a median value of 0.41 pg TEQ/g using the Upper Bound approach[7]. Levels of dioxins in (cow) milk in the USA were averaged from the data at Chemical Contaminants > Non-TDS Foods Analyzed for PCDD/PCDFs in 2001-2003 (archive-it.org), which shows the PCDD/PCDF summary and congener files for non-TDS foods analyzed in FY 2001-2003. The Upper Bound level was 0.58 pg/g fat in whole milk (4.0% fat).

Dioxin levels in the three batches of Dry Whole Goat Milk (DWGM) are all well within the food grade specifications regardless of the manner of handling non-quantified congeners as shown in Table B.2.

Table B.2. *Analysis of Dioxins, Furans and dl-PCBs in Three Non-Consecutive Lots Dry Whole Goat Milk in WHO-PCDD/F PCB TEQ (pg TEQ/g fat)*

Parameter	Specification	Lot 1	Lot 2	Lot 3	Average	Method
TEQ (pg TEQ/g fat)	< 4.0					
Upper Bound Level		0.44	0.35	0.37	0.39	Conform EU 644/2017
Upper Bound Level divided by square root of two		0.31	0.25	0.26	0.27	Calculation
Lower Bound Level		0.28	0.14	0.20	0.21	Conform EU 644/2017

Dioxin levels in human milk are 1-2 orders of magnitude higher than levels in infant formula[60,67]. Dioxins in milk of Canadian[68], Swedish[69], Japanese[70] and Dutch[71] mothers are consistent with global trends of reductions since the 1990s[60]; available evidence suggests similar temporal decreases in the US, despite the absence of nationally representative data [72].

Pandelova et al.[62] obtained and composited samples representing cow milk-based, soy-based and hypoallergenic formulas from six countries in Europe. They reported levels of dioxins, furans, and dioxin-like PCBs as dry weights: 0.01-0.11 pg TEQ/g as dry-weight powder dioxins and furans, 0.0003-0.001 pg TEQ/g dry as dioxin-like PCBs. As formulas are about 25% fat by weight, these values approximate 0.45 pg TEQ/g fat. In the UK a decline was reported in measured upper-bound dioxin TEQs in milk and soy-based formula between 1998 and 2003. They reported the following concentration ranges for 1998 and 2003, respectively: 0.5-3.1 pg TEQ/g lipid and 0.2-0.4 pg TEQ/g lipid.

Calculating the level of dioxins, furans, and dl-PCBs in DWGM (42%)-based infant formula with 26% fat, leads to an Upper Bound level of 0.19 pg TEQ/g fat in the formula (0.12 for the Lower Bound level)[3].

The TEQ from DWGM can be calculated as follows:

> DWGM is proposed to be one of the many ingredients used to comprise an intact infant formula. This notification specifies the maximum amount of DWGM at 42% of powdered infant formula (g/g). Nutrient requirements for infant formula are expressed on a per 100 kcal basis; powdered infant formula has a caloric density of 20g/100 kcal. Therefore, DWGM is intended to be used at the rate of 8.4 g/100 kcal. The DWGM specification for fat is from 26% to 35% with a typical value of 32%. So the DWGM will provide from 2.2 to 2.9g fat/100 kcal. This amount of fat in DWGM would deliver 0.39 pg TEQ/g * (2.2 or 2.9 g fat) or 0.9-1.1 pg TEQ/100 kcal, using the Upper Bound, from Table 2, to 0.21 pg TEQ * (2.2 or 2.9 g fat) or 0.5- 0.6 pg TEQ/100 kcal, using the Lower Bound, Table 2. The typical fat level in DWGM (32%) and the square root * Upper Bound to account for lower than LOQ values gives an estimate of 0.27 pg TEQ/g * 2.72 g fat, or 0.7 pg/100 kcal.

The additional fat used in manufacturing infant formula is vegetable oils, which were reported to contain 0.2 pg TEQ/g fat[73]. To reach the minimum fat required when the lowest in-specification level of fat in DWGM is used (26%), an additional 1.1 g of fat would need to be added contributing 0.2 pg TEQ, bringing the total to 1.1 pg TEQ; the highest in-specification fat (35%) would require a minimum of 0.4 g additional fat from vegetable oils contributing 0.1 pg, bringing the total to 1.2 pg TEQ/100 kcal. Using the upper bound for the calculations, thus, results in 1.1 to 1.2 pg TEQ/100 kcal. The corresponding estimate derived from using Lower Bound TEQ is 0.6 to 0.7 pg TEQ/100kcal.

The energy requirements in infancy are about 100kcal/kg in the first few months and decrease thereafter (IOM 2002),[4] so the per kg exposure is between 0.6 and 1.2 pg TEQ in the first 3 months of life; 0.5- 1.0 pg TEQ from 4-6 mo, and 0.5-1.0 pg TEQ from 6-12 months.

Exposure of infants to dioxins

Standards for dioxin exposure

In 2002, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable intake of 70 pg/kg body weight per month for PCDDs, PCDFs, and coplanar PCBs expressed as TEFs. The value is expressed per month to reflect that exposure is cumulative and chronic rather than acute[74].

In 2012, the US EPA[58] set a maximum per day of 0.7 WHO-PCDD/F PCB TEQ/kg. This Reference dose (RfD) for oral exposure for TCDD[75,76] (which can also be applied to dioxin TEQs) is based on decreased sperm count and motility in adult human males who were exposed to TCDD during childhood and is supported by evidence of potential susceptibility during infancy and is relevant for use in risk assessments of early life exposures. The lowest-observed-adverse-effect-level (LOAEL) is 20 pg/kg per day.

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[3] The Upper bound level in DWGM is 0.39 pg TEQ/g fat, Lower Bound level is 0.25. In the powdered infant formula 42% of DWGM with 30% milk fat is used; the formula has 26% fat (originating from both the DWGM and additional vegetable oils). (30%*42)/26*level in DWGM = pg TEQ/g fat in the formula.

[4] (p 169) EER for Ages 0 Through 36 Months
EER = TEE + energy deposition
0–3 months (89 × weight [kg] – 100) + 175 kcal
4–6 months (89 × weight [kg] – 100) + 56 kcal
7–12 months (89 × weight [kg] – 100) + 22 kcal

In 2018, EFSA's expert Panel on Contaminants in the Food Chain (CONTAM)[67] published a comprehensive review of the risks to human and animal health from dioxin and dioxin-like PCBs in food and feed.

The EFSA Panel set a new tolerable weekly intake [TWI] for dioxins and dioxin-like PCBs in food of 2 picograms per kilogram of body weight. This TWI is seven times lower than the previous EU tolerable intake set by the European Commission's former Scientific Committee on Food in 2001.

The TWI of 2 pg per kg bw is derived when taking exposure via breastfeeding in the first year of life into account, 165 TEQ/d (800 mL milk/day, 3.5% milk fat, 5.9 pg TEQ/g milk lipid)[67]. The Health Based Guidance Value (HBGV) was based on a serum level of 7 pg PCDD/PCDF/g serum lipid that modeling predicts would be reached at the age of 9 years, i.e., the age at which disturbed spermatogenesis at adult age is induced. The modeling accepts current exposures at birth (from maternal body fat levels) and from breastfeeding (165 pg/TEQ/d, assuming 800 ml milk/d, 3.5% milk fat, and 5.9 TEQ/g lipid) as negligible risks[71].

Dioxin exposure from DWGM in infant formula

A 1-month-old boy at the 90th percentile bw (5.2kg), drinking 900 mL of goat milk-based infant formula per day, ingests an estimated amount of 1.1 pg TEQ/kg bw per day[5] when the exposure is calculated with the maximum level of the Upper Bound Levels in the goat milk powders. In Table B.3. the calculated exposure for this extreme 1-month-old is shown as well as the calculated exposure for a 3-4 months infant of 6.4 kg (average bw at 50th percentile) drinking 787 mL [62] of infant formula per day.

[5] The estimated exposure in pg TEQ/kg bw per day is calculated as follows: 5.5 g DWGMP (with 30% fat) per 100 ml formula, 900 mL consumed: 5.5/100 * 900 * 30% = 14.9 g milk fat per day. Milk fat per day * pg TEQ/g fat = 14.9 * 0.4 = 5.9 *what is the 0.4 value? pg TEQ per day. Divided by 5.2 kg: 5.9 / 5.2 = 1.1 pg TEQ/kg bw per day.

Table B.3. *Calculation of WHO-PCDD/F PCB TEQ (pg TEQ/kg bw) exposures from DWGM in an infant formula.*

	RfD (US EPA 2012) And TWI (EFSA)	Upper Bound Level	Upper Bound Level* square root of two^{-1}	Lower Bound Level
WHO-PCDD/F PCB TEQ (pg TEQ/kg bw) exposures from DWGM for a 1-month-old boy at the 90th percentile bw (5.2kg), drinking 900mL of goat milk-based infant formula per day	0.7	1.1	0.8	0.7
WHO-PCDD/F PCB TEQ (pg TEQ/kg bw) exposures from DWGM for an infant of 6.4kg, drinking 787mL of goat milk-based infant formula per day	0.7	0.9	0.6	0.6

Total infant diet

For infants consuming ‘‘starting” milk, soy, or hypoallergenic infant formula in their early life after birth until 4th month, dietary exposure may exceed the lowest range of the TDI of PCDD. In particular in infants fed only ‘‘starting” hypoallergenic infant formula, dietary exposure to PCDD/D and PCB may achieve values of 2.8 pg WHO-TEQ / kg bw per day and 84 pg WHO-TEQ / kg bw per month [62].

Table B.4. *Estimated dietary exposure to PCDD/F and PCB (pg WHO-TEQ/kg bw per day) for infants 0-9 months of age fed with infant formulae available on the EU market.*

Type infant formula	Infant age (month)								
	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9
PCDD/F WHO-TEQ (pg kg^{-1} bw) d^{-1}									
Mf	1.01	0.92	0.84	0.73	0.51	0.32	0.18	0.18	0.17
Sf	1.26	1.15	1.05	0.91	0.26	0.16	0.09	0.09	0.09
HAf	2.78	2.52	2.31	2.01	0.13	0.08	0.05	0.04	0.04
PCB WHO-TEQ (pg kg^{-1} bw) d^{-1}									
Mf	0.03	0.02	0.02	0.02	0.04	0.02	0.01	0.01	0.01
Sf	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00
HAf	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.00

Source: Pandelova et al, 2010[62]. Mf = milk-based infant formula, Sf= soy-based infant formula, and HAf = hypo-allergenic infant formula

When comparing the values from the 3-4 months-old from Table 5 with the daily exposures from Table 4, the exposure per day from the DWGM in a goat-milk based infant formula would be very similar to those values.

Weijs et al.[73] assessed the food intake of 188 infants by a 2-d food record and from these data PCDD/F and dioxin-like PCB intake was calculated using PCDD/F and dioxin-like PCB concentrations of food products sampled in 1998/1999 in The Netherlands. The long-term PCDD/F and dioxin-like PCB exposure of the infants was calculated using the statistical exposure model (STEM). For infants of 5 months, the chronic exposure to PCDD/F and dioxin-like PCB was 1.1 pg WHO-TEQ per kg bw per day (95th percentile: 1.7 pg WHO-TEQ/kg bw per day), which mainly originated from cow milk based infant formula and vegetables and increased to 2.3 pg WHO-TEQ/kg bw per day (95th percentile 3.7 pg WHO-TEQ/kg bw per day) for infants just over 1 year old eating the same food as their parents. These calculations using data from 1998/9 likely overestimate exposures today; based on the reductions in

human milk in that time frame, todays estimates would be expected to be only about a third of the 1998 levels.

Other GRAS Notifications

The only current GRAS notification with goat milk, GRN 644 'Nonfat Dry Goats' Milk and Goat Whey Protein Concentrate in Infant Formula'[4], does not discuss dioxin though it is included in a blanket statement on the goat milk; "the goat milk is in compliance with the hygiene requirements of The Netherlands and the European Union with an adequate monitoring program based on risk analysis".

GRNs on dry whole cow milk GRN 980[6] and GRN 1041[5] do not provide a safety assessment regarding dioxin levels. However, the usage levels of total milk, and thus milk fat in powdered formulas described in those notifications are lower than the use level for Jovie: respectively 21% of fat in the formula is provided by dry whole milk in GRN 1041 and max 16% of DWM in the powdered IF in GRN 980 which calculates to about 18% of the fat in the formula provided by DWM. Jovie's formulation with 42% of DWGM provides about 48% of the fat in the formula.

FDA Form 3667

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
001136	02/23/2023
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):* _____

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
H.H. Wemekamp-Kamphuis	Dr.
Organization *(if applicable)*	
Jovie USA LLC	
Mailing Address *(number and street)*	
1600 Golf Road Corporate Center, Suite 1200	

City	State or Province	Zip Code/Postal Code	Country
Rolling Meadows	Illinois	IL60008	United States of America

Telephone Number	Fax Number	E-Mail Address
+1 833 USAGOAT		h.wemekamp@jovieusa.com

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

Name of Contact Person	Position or Title
Organization *(if applicable)*	
Mailing Address *(number and street)*	

City	State or Province	Zip Code/Postal Code	Country

Telephone Number	Fax Number	E-Mail Address

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

Dry Whole Goat Milk

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

☒ Electronic Submission Gateway

☐ Electronic files on physical media

☐ Paper

If applicable give number and type of physical media

_____

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

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

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

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

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

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

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

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

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

Dry Whole Goat Milk is intended to be used as the source of protein in infant formula for full-term gestation infants (>37 weeks of gestational age) up to 12 months of age. The common protein concentration in an infant formula of 2.1 g protein/100kcal, would typically need 42 g Dry Whole Goat Milk per 100g powdered infant formula.

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 H.H. Wemekamp-Kamphuis *(name of notifier)*

has concluded that the intended use*(s)* of Dry Whole Goat Milk *(name of notified substance)*

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

2. H.H. Wemekamp-Kamphuis *(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.

1600 Golf Road Corporate Center, Suite 1200. Rolling Meadows IL60008 *(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)
	H.H. Wemekamp-Kamphuis	02/16/2023

SECTION G – LIST OF ATTACHMENTS

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

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Form3667_GRASDryWholeGoatMilk_2023-02-16	Administrative
	CoverLetter_GRASDryWholeGoatMilk_2023-02-16	Administrative
	GRASNotice_DryWholeGoatMilk_2023-02-16	Submission

From: Henrike Wemekamp - Jovie USA
To: Morissette, Rachel
Subject: [EXTERNAL] RE: RE: RE: questions for GRN 001136
Date: Thursday, August 31, 2023 12:04:26 PM
Attachments: 16c735734be3140ac622b533d2aacb21-522309b50df189ab1d7575b157ca5e7b90896398.png
24900c20a42baca832515bbdd1f63195.png
a3640b56d10be53999f7d5efa2fe7e10.png
585143d805fa42e0ddf46d2de57aa3ac.png
ff38b409a791af294626de6339b0120e.png
fa2baa4ea04279d280528f2aeb2ab39a.png
ede284eb4bf2518fd46ae9abe1e10fe9.png
16c735734be3140ac622b533d2aacb21.png
24900c20a42baca832515bbdd1f63195.png
a3640b56d10be53999f7d5efa2fe7e10.png
585143d805fa42e0ddf46d2de57aa3ac.png
ff38b409a791af294626de6339b0120e.png
fa2baa4ea04279d280528f2aeb2ab39a.png
ede284eb4bf2518fd46ae9abe1e10fe9.png
2023 08 30 questions for notifier GRN 001136 RESPONSE.pdf

Dear Dr. Morissette, Hi Rachel,

Please find attached our responses to your questions on Jovie's GRAS notice GRN 001136 for the intended use of dry whole goat milk (DWGM).

Best,
Henrike

Henrike Wemekamp-Kamphuis

Jovie USA LLC
1600 Golf Road Corporate Center, Suite 1200
Rolling Meadows, IL60008
United States of America

Tel: +1 886 4523582 (general)
Tel: ++1 866 2729518 (logistics)
Website: www.jovieusa.com
Mob: +31 6 22053364

----- Oorspronkelijk bericht -----
Van: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Aan: "Henrike Wemekamp - Jovie USA" <h.wemekamp@jovieusa.com>
Datum: 25 augustus 2023 15:37
Onderwerp: RE: [EXTERNAL] RE: questions for GRN 001136

Hi,

Yes, the 31st will be fine.

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

From: Henrike Wemekamp - Jovie USA <h.wemekamp@jovieusa.com>
Sent: Thursday, August 24, 2023 11:16 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: [EXTERNAL] RE: questions for GRN 001136

Dear Rachel,

Herewith I would like to confirm we received your email and the questions for GRN 001136.
As we have received the underneath email on the 17th of august, I would like to ask you to confirm it is ok that we will reply within 10 business days of this day, on the 31st of august.
I'd like to confirm with you as the letter is dated on the 15th of august.

Best regards,
Henrike

Henrike Wemekamp-Kamphuis, Ph.D.

Jovie USA LLC
1600 Golf Road Corporate Center, Suite 1200
Rolling Meadows, IL60008
United States of America

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----- Oorspronkelijk bericht -----
Van: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Aan: "Henrike Wemekamp - Jovie USA" <h.wemekamp@jovieusa.com>
Datum: 17 augustus 2023 17:12
Onderwerp: questions for GRN 001136

Dear Dr. Wemekamp-Kamphuis,

Please see attached our questions for GRN 001136. Let me know if you have questions at this time.

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
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To
Rachel Morissette, Ph.D.
Division of Food Ingredients
Center for Food Safety and Applied Nutrition

August 30th, 2023

Regarding: GRAS Notice No. GRN 001136

Dear Dr. Morissette,

Please find below our responses to your questions on Jovie's GRAS notice GRN 001136 for the intended use of dry whole goat milk (DWGM).

Chemistry:

Intended use

1. Please clarify if DWGM is limited to use in goat-milk-based infant formulas only or if use in other protein bases is expected.

   At this time the only intended use is goat milk-based infant formulas.

2. On p.13 of the notice, the intended use of DWGM in non-exempt infant formula is described to be at a minimum level of 35 g DWGM/100 g of formula powder, at a typical level of 42 g/100 g, and at a potential maximum level of 88 g/100 g based on the specified range for protein composition of infant formula listed in 21 CFR 107.100. On p.29 of the notice, the GRAS panel's conclusion refers to the maximum use level as 45 g DWGM/100 g formula powder. Please clarify the maximum intended use level of DWGM in infant formula.

   The GRAS notice is written on a maximum intended use level of 42 g DWGM/100 g formula powder.

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Composition

3. On p.26 of the notice, the suitability of DWGM as a source of fat in infant formula is discussed, including a comparison of the fatty acid compositions of DWGM to cow milk and human milk based on published information (Gallier et al., 2020). Please discuss the suitability of DWGM as a source of fat in infant formula with respect to other lipid constituents, such as cholesterol, phospholipids, sphingolipids, and components of the milk fat globule membrane.

Human, cow and and goat milk contain similar levels of cholesterol, total phospholipids, and subgroups of phospholipids including sphingolipids (Gallier et al. 2020). This has been confirmed in a more recently published research (Magnuson et al. 2022). Milk fat globule membrane composition of fatty acids in goat milk is more like that of human milk than is cows milk; the former two have predominance of oleic acid whereas palmitic acid is the predominant fatty acid in cows milk MFGM (Sun et al. 2022). Prosser cited two publications reporting that the major protein composition of human, goat and cow milk globule membranes was similar (Prosser, 2021).

Specifications

4. On p.12 of the notice, Jovie states that the goat milk used to produce DWGM is monitored twice per year for potential contaminants, including heavy metals, aflatoxin B1, polychlorinated biphenyls (PCBs), dioxins, pesticides, and veterinary drugs to ensure DWGM is food-grade and meets European Union specifications. Appendix B of the notice includes additional discussion of potential dietary exposures to dioxins, furans, and dioxin-like PCBs. Please note that standards and regulations for environmental contaminants, animal drugs, and pesticides in foods such as milk are outlined in 21 CFR 109.30 (tolerances for PCBs), 21 CFR Part 556 (tolerances for residues of new animal drugs in food), and 40 CFR Part 180 (tolerances for pesticides in food and feed). FDA also has action levels for several pesticides (listed in Compliance Policy Guide (CPG) section 575.100) and for aflatoxin M1 (CPG Section 527.400). In addition to tolerances and action levels, FDA also may use "target testing levels" as guidelines for certain drug residues, including those with a tolerance of zero in milk (e.g., erythromycin, penicillin). In accordance with Appendix N of the Pasteurized Milk Ordinance (PMO), target testing levels have been communicated via a Memoranda of Information (M-I) from FDA, most recently M-I-18-9, issued February 12, 2018. The PMO is the milk sanitation standard for Grade "A" milk and milk products used by the National Conference on Interstate Milk Shipments program. Please confirm the following:

   a. The starting material for DWGM is produced in accordance with good agricultural practices and meets applicable U.S. regulations.

   We confirm the DWGM is produced in accordance with good agricultural practices that apply equally to cows milk and goat milk. The DWGM conforms to international standards and U.S. regulations for environmental contaminants, animal drugs and pesticides. EU regulations are described in, among others, Regulation (EC) No 315/93 for contaminants

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in food, No 396/2005 (EU legislation on MRLs (europa.eu)) on residue levels of pesticides and No 470/2009 (EUR-Lex - mi0026 - EN - EUR-Lex (europa.eu)) and No 37/2010 (EUR-Lex - 32010R0037 - EN - EUR-Lex (europa.eu)) on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin.

b. The starting material for DWGM complies with derived intervention levels for radionuclides (CPG 555.880).

The purpose of CPG 555.880 is to present guidance levels for radionuclide activity concentration, called derived intervention levels (DILs). These were initially proposed to manage food-based exposures following nuclear accidents. Similar specifications exist in Europe (EU 2016/52). Foods in Europe, including milk, are monitored for radionuclides even in the absence of nuclear accidents, and radionuclides levels have been reported at levels far below the DILs. For example, results of the monitoring program of the Dutch dairy industry show values of <10 Bq/kg milk over the years 2012 – 2017 for both median and maximum values for Cesium-134 + Cesium-137 (GRAS Notice 898, Steinborn 2019), orders of magnitude lower than the DIL.

c. The starting material for DWGM meets pesticide tolerances specified in 40 CFR Part 180 for milk and milk fat.

The DWGM conforms to international standards and U.S. regulations for environmental contaminants, animal drugs and pesticides. For pesticide tolerances, EU regulations are described in Regulation EC No 396/2005.

d. The starting material for DWGM meets U.S. regulatory limits for veterinary drug residues in milk and milk fat, and pesticides, and is tested regularly for contaminants as outlined in the Grade "A" PMO.

In Europe the dairy chain works according to regulations based on the European Regulation No. 178/2002, known as the General Food Law (GFL). This includes Regulation No. 853/2004, laying down specific hygiene rules for food of animal origin.
Based on the above, we confirm that the goat milk meets the regulatory limits for veterinary drug residues in milk and milk fat and pesticides as outlined in the Grade 'A' PMO.

5. On p.7 of the notice, Jovie states that DWGM is analyzed for ash; however, there is no corresponding specification provided in Table 1 (p.9). Please clarify whether Jovie has specified a limit for ash, and if so, provide the results from a minimum of three non-consecutive batch analyses.

There are no specific minimum and maximum values for ash needed, hence there is no ash specification.

6. Table 3 (p.11) includes the results of batch analyses for lactose and various minerals (sodium, potassium, manganese, magnesium, etc). Please clarify if acceptable limits for the concentration of these constituents in DWGM have been established.

   The certificate of analysis for the DWGM ingredient does not have specifications for lactose or these minerals. The data in the GRAS notification provide lactose and mineral values that inform manufacturers of approximate levels. All these mineral elements have specifications in the infant formula and manufacturers often include other ingredients to provide the required levels of these minerals.

7. The specified maximum limit for nitrate in DWGM is listed as <50 mg/kg in Table 1 (p.10); however, the specification listed in Table 3 (p.11) is <100 mg/kg. Please clarify the specification for nitrate.

   Two different specifications for nitrate are mentioned: the regulatory 'Reference' specification Standard (<100 mg/kg) and the ingredient supplier specification (<50 mg/kg). We have cited the regulatory 'Reference' specification standard in table 3. We agree with you that it would have been more logical to cite our ingredient supplier specification (<50 mg/kg) in Table 3. The supplier has a more stringent specification.

8. The specifications provided for titratable acidity in Table 1 (p.9) and Table 3 (p.11) are listed as ≤18%; however, the units are also listed as "mL 0.1 N NaOH/10 g solids-not-fat" in the same tables. Please clarify the correct units for the titratable acidity specification.

   As you have correctly noticed, the '%' mark should be deleted in the display of the specification value. The values for Titratable acidity are all indicated in 'mL 0.1 N NaOH/10 g solids-not-fat'.

9. A specification for total chromium is provided in Table 1 (p.9); however, we note that the results of the batch analyses (Table 3, p.11) do not include the results for chromium. Please provide the results from a minimum of three non-consecutive batch analyses for chromium.

   Please find the results for chromium of three non-consecutive batches in the table underneath.

Parameter	*Specification*	*Lot 1*	*Lot 2*	*Lot 3*
Chromium (total) (mg/kg)	<2	< 0.05	< 0.05	< 0.05

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10. A specification for *Cronobacter* spp. is provided in Table 2 (p.10); however, we note that the results of the batch analyses (Table 3, p.11) do not include the results for *Cronobacter* spp. Please provide the results from a minimum of three non-consecutive batch analyses for this microorganism. Further, we note that the method cited is ISO 22964 and that the sample batch size is 100 g (3 samples). We note a discrepancy in that this method is validated for test sample sizes of 10 g. Please clarify whether the method is validated for larger sample sizes.

Please find the results for *Cronobacter* spp. of three non-consecutive batches Dry Whole Goat Milk in the table underneath. The method is validated for the larger sample size and the laboratory is accredited for this test.

Parameter	*Lot 1*	*Lot 2*	*Lot 3*
Cronobacter (/100g, n=3)	negative	negative	negative

11. In Table 1 (p.9), specification limits for heavy metals are provided and the results of batch analyses are provided in Table 3 (p.11), demonstrating that all batches are within the specified maximum and below the typical value in Table 1. Please state the limits of quantitation for the methods of analyses used for heavy metals. Specifications help to ensure that the ingredient is manufactured in accordance with good manufacturing practices, and we note FDA's recent "Closer to Zero" initiative focuses on reducing dietary exposure to heavy metals from food. Please consider adjusting the specified limits for these metals to align with the results of the batch analyses and the limits of quantitation. For example, the limit for arsenic is <0.1 mg/kg with batch results consistently <0.03 mg/kg, whereas lead has a higher limit of <0.15 mg/kg even though batch analyses are consistently <0.02 mg/kg.

Please find the limits of quantification for the methods of analyses for heavy metals in the table underneath.

Parameter	*unit*	*Limit of quantification*
Lead	mg/kg	0.02
Cadmium	mcg/kg	2
Arsenic	mcg/kg	30
Chromium	mg/kg	0.05
Mercury	mcg/kg	1

The values for the three non-consecutive batches shown in table 3 all indicate the limit of quantification, no measureable amounts of heavy metals were found.
In the closer to zero program, FDA excluded infant formula from its recently published Action levels for Lead in Food Intended for Babies and Young Children.

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The batch results show consistent significantly lower levels than the specification, which should assist infant formula manufacturers to produce finished products with low heavy metal exposures from infant formula.

Dietary Exposure

12. The notice includes estimates of dietary exposure to DWGM for infants at 1 month of age based on published estimates of infant dietary energy requirements. However, the notice does not include the estimated dietary exposure to DWGM for other infant age groups that are within the expected consumer population (e.g., infants up to 12 months of age). Please provide estimates of dietary exposure to DWGM based on the maximum intended use level and infant formula consumption in the U.S. throughout infancy that represents the intended population of male and female infants and all ages (e.g., infants from birth to 6 months and 7 to 12 months of age).

As the energy requirement per kg body weight are the highest for small infants, these data were used in the notice. Butte (2005) provides the underneath data for energy requirements for all infants 0-12 months of age. From this, DWGM intake per kg body weight can be calculated. However, the table below shows the exposure for an unrealistic situation when the only food consumed is formula.

Energy requirement in kcal/kg/day for boys and girls (Butte, 2005) and subsequent DWGM intake for boys and girls from 1 to 12 months.

Age (months)	Boys (kcal/kg/day)	Girls (kcal/kg/day)	Boys DWGM intake[a] (g DWGM/kg/day)	Girls DWGM intake[a] (g DWGM/kg/day)
1	113	107	9.4	8.9
2	104	101	8.6	8.4
3	95	94	7.9	7.8
4	82	84	6.8	7.0
5	81	83	6.7	6.9
6	81	82	6.7	6.8
7	79	78	6.6	6.5
8	79	78	6.6	6.5
9	79	78	6.6	6.5
10	80	79	6.6	6.6
11	80	79	6.6	6.6
12	81	79	6.7	6.6

[a]example calculation for the mean DWGM intake for a boy of 1 months of age: 113 kcal/per day is 22.3g (122/506 x 100) powdered infant formula. The powdered infant formula contains maximum 42% DWGM, thus 9.4 g (42% x 22.3g).

Infants start to receive solids in the range from 4 to 6 months, so not all energy after 4 to 6 months comes from formula. AAP states “By 6 months your baby will consume 6 to 8 ounces (180–240 mL) at each of 4 or 5 feedings in 24 hours[a]”.

[a]This does not consider differences between boys and girls, the girls consuming smaller amounts than boys

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This calculates to an average of 7 ounces *4.5 feedings = 31.5 ounces, which calculates to 51 g DWGM (31.5*29.6 = 932 mL. 13% formula powder * 932 = 121g formula, which is 42%*121g = 51 g DWGM). For a 6-month old boy of an average weight (7.9 kg; CDC growth charts Growth Charts - Data Table of Infant Weight-for-age Charts (cdc.gov)), the exposure calculates to 6.4 g DWGM/kg/day.
From 9 to 12 months, babies should continue to have about 7 to 8 ounces of liquid per feeding. They usually cap out at 32 ounces of formula in 24 hours Baby Feeding Chart: How Much Infants Eat in the First Year (parents.com). Calculating with this maximum of 32 ounces of formula (947 mL), the exposure for a 12-month old boy (10.3 kg) is 5.0 g DWGM/kg/day, almost half of the exposure at 1 month.
Similarly, for 6-month old girls (7.2 kg) on the 50th percentile (CDC growth charts on cdc.gov), the exposure calculates to 7.1 g DWGM/kg/day and for a 12-month old of 9.6 kg, 5.4 g DWGM/kg/day. From these data it shows that exposure per kg body weight goes down over age.

Toxicology:

13. The GRAS Final Rule (81 FR 54960-55055) states that the safety narrative should include "a comprehensive discussion of any reports of investigations or other information that may *appear* to be inconsistent with the GRAS determination..." (emphasis added). In this context, please provide a discussion on the following:
    a. While Jovie states on p.13 of the notice "no commercial formula contains the maximum protein concentration" of 4.5 g/100 kcal, Jovie does not discuss how the proposed use (with maximum level of 2.1 g protein/100 kcal) is not expected to be a safety concern, given reports of adverse effects, such as metabolic acidosis, from infants consuming undiluted goat milk (Basnet et al., 2010; Prosser, 2021).

       Feeding (fresh) undiluted goat milk or cow milk to infants is not relevant to the intended use of DWGM in manufacture of infant formula. The nutritional components that dispose to risk of metabolic acidosis as described in Basnet et al. (2010) and Prosser (2021), ie high levels of protein and minerals are all controlled by regulation in infant formula.

    b. Jovie notes that in Zhou et al. (2014), a statistically significant higher rate of blood-stained stools was noted in infants consuming goat milk-based infant formula (using whole goat milk) compared to those consuming cow milk-based infant formula. Although this finding did not seem to be observed in other infant studies with goat milk-based infant formula (e.g., He et al. 2022), it is also not clear from the discussion what type of goat milk (whole vs. skimmed milk) was used in these later studies. Please clarify the relevance of these clinical studies with respect to the test formula used in comparison to Jovie's proposed use/use level.

       Grant et al. (2005), studied goat milk-based infant formula produced by Dairy Goat Co-operative (N.Z.), known for their whole goat milk-based infant formulas. Using the same

supplier Zhou et al. (2014) indicates the use of whole goat milk in the studied infant formula. Xu et al. (2015) and He et al. (2022), used preparations of goat milk protein; protein being the component that is considered the agent responsible for blood in stools. A more recently published systematic review and meta-analysis by Jankiewicz et al. (2023) supports the conclusions made in GRN 1136, that DWGM is safe for use in infant formulas. The four RCTs selected in this paper were the same as the ones listed in the current GRAS notification. The authors concluded that adverse effects (serious or any) were similar in the goat milk-based infant formula and cow milk-based infant formula groups.

14. Jovie states on p.19 of the notice "The detection of blood-in-stools is not uncommon in cow's milk formula-fed infants and therefore not surprising to be found in goat milk formula-fed infants." Please provide a basis for this statement, as it is not clear how the citation listed supports this statement.

The cited EFSA Scientific Opinion (2012) states "There was no difference in the occurrence of serious adverse events in the two groups of formula-fed infants during 12 months". The occurrence of blood-in-stools was called to the attention of the GRAS panel. Pediatricians on the GRAS panel, including a pediatric allergist, stated blood-in-stools is not uncommon and expressed no concerns over safety related to the report of bloody stools by Zhao et al.
The statement that the detection of blood-in-stools is not uncommon in infants is further supported by a recently accepted ESPGHAN position paper stating that "…occasional spots of blood in stool are common and in general should not be considered as diagnostic of CMA (cow's milk allergy), irrespective of preceding consumption of cow's milk" (Vandenplas et al., 2023).

15. It is not clear if an updated literature search and evaluation were conducted. For example, we note that Prosser (2021) was not included in the citations in the notice. Please provide information on Jovie's literature search, including databases used, search terms, and dates conducted, as well as a discussion of any new publications with relevance to the safety assessment.

As the R&D for infant formula development, we keep track of the relevant literature (with search terms 'goat' and/or 'infant' and/or 'formula') continuously within databases PubMed and search engine Google Scholar. We have monitored the literature in specific aspects and were attentive to safety concerns (eg the bloody stools). We are aware of the article of Prosser (2021) and have discussed the relevant items in this manuscript in the GRAS. Prosser (2021) is a review and we relied on the relevant primary literature that was reviewed by Prosser.

16. Please discuss the whey-to-casein ratio of DWGM and how that may affect the intended conditions of use. For example, it is not clear from the intended use whether or not there will be a modification to the whey:casein ratio in the final infant formula product. Furthermore, we note that goat milk contains a number of oligosaccharides identical to human milk oligosaccharides (Prosser, 2021). While the final formulation is the responsibility of the infant formula manufacturer,

please clarify that if your ingredient is used, addition of other ingredients, including whey fraction and/or indigestible oligosaccharides, would not alter the safety profile of Jovie's article of commerce.

The intended use of DWGM in non-exempt infant formula assumes the whey to casein ratio of DWGM. We are not aware of any safety concerns related to the whey to casein ratio. A separate GRN with a different whey to casein ratio also was determined to be safe to use in non-exempt infant formula (GRN 644).
Addition of other oligosaccharides to an infant formula is beyond the scope of this GRAS notification.

Kind regards,

Henrike Wemekamp-Kamphuis, Ph.D.
Manager Research & Development
Jovie USA LLC

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