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#899

By Federal Express

November 7, 2019

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

Re: GRAS Notice for the Use of Citric Acid Esters of Mono- and Diglycerides (CITREM) in Exempt Infant Formula for Term Infants

Dear Sir or Madam:

We hereby submit the enclosed GRAS notice for CITREM as an ingredient in exempt infant formula. The proposed use of CITREM is as an emulsifier at a maximum level of 233 mg per 100 mL (2330 mg per L or 0.233%) in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction. Hogan Lovells US LLP's conclusion of GRAS status for the intended use of CITREM is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

CITREM is not intended for use in any products that would require additional regulatory review by the United States Department of Agriculture. The GRAS notice does not contain any designated confidential business information. In accordance with the Agency's guidelines, we have enclosed Form 3667, one original copy of the GRAS notice, and one complete electronic copy of the GRAS notice on a compact disk (CD).

We are committed to cooperating with the Agency and believe an open dialog is one of the most effective ways to accomplish that objective. If any questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

If you have any questions, please contact us.

Sincerely,

Steven B. Steinborn
steven.steinborn@hoganlovells.com
202 637 5969

Xin Tao
xin.tao@hoganlovells.com
202 637 6986

Form Approved: OMB No. 0910-0342; Expiration Date: 09/30/2019
(See last page for OMB Statement)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000899	Jan 9, 2020
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

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

SECTION A – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

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

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

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

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
Steven B. Steinborn	Partner
Organization *(if applicable)*	
Hogan Lovells US LLP	
Mailing Address *(number and street)*	
555 13th St, NW	

City	State or Province	Zip Code/Postal Code	Country
Washington	District of Columbia	20004	United States of America

Telephone Number	Fax Number	E-Mail Address
202 637 5969	202 637 5910	steven.steinborn@hoganlovells.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

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

Citric Acid Esters of Mono- and Diglycerides (CITREM)

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

1 CD

3. For paper submissions only:

Number of volumes _____

Total number of pages _____

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

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

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

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

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

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

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

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

☐ Yes *(Proceed to Item 8*

☒ No *(Proceed to Section D)*

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

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

☐ No

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

☐ Yes, a redacted copy of the complete submission

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

☐ No

SECTION D – INTENDED USE

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

The proposed use of CITREM is as an emulsifier at a maximum level of 233 mg per 100 mL (2330 mg per L or 0.233%) in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction.

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 Hogan Lovells US LLP
(name of notifier)

has concluded that the intended use*(s)* of Citric Acid Esters of Mono- and Diglycerides (CITREM)
(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. Hogan Lovells US LLP 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.
(name of notifier)

555 13th St, NW; Washington DC
(address of notifier or other location)

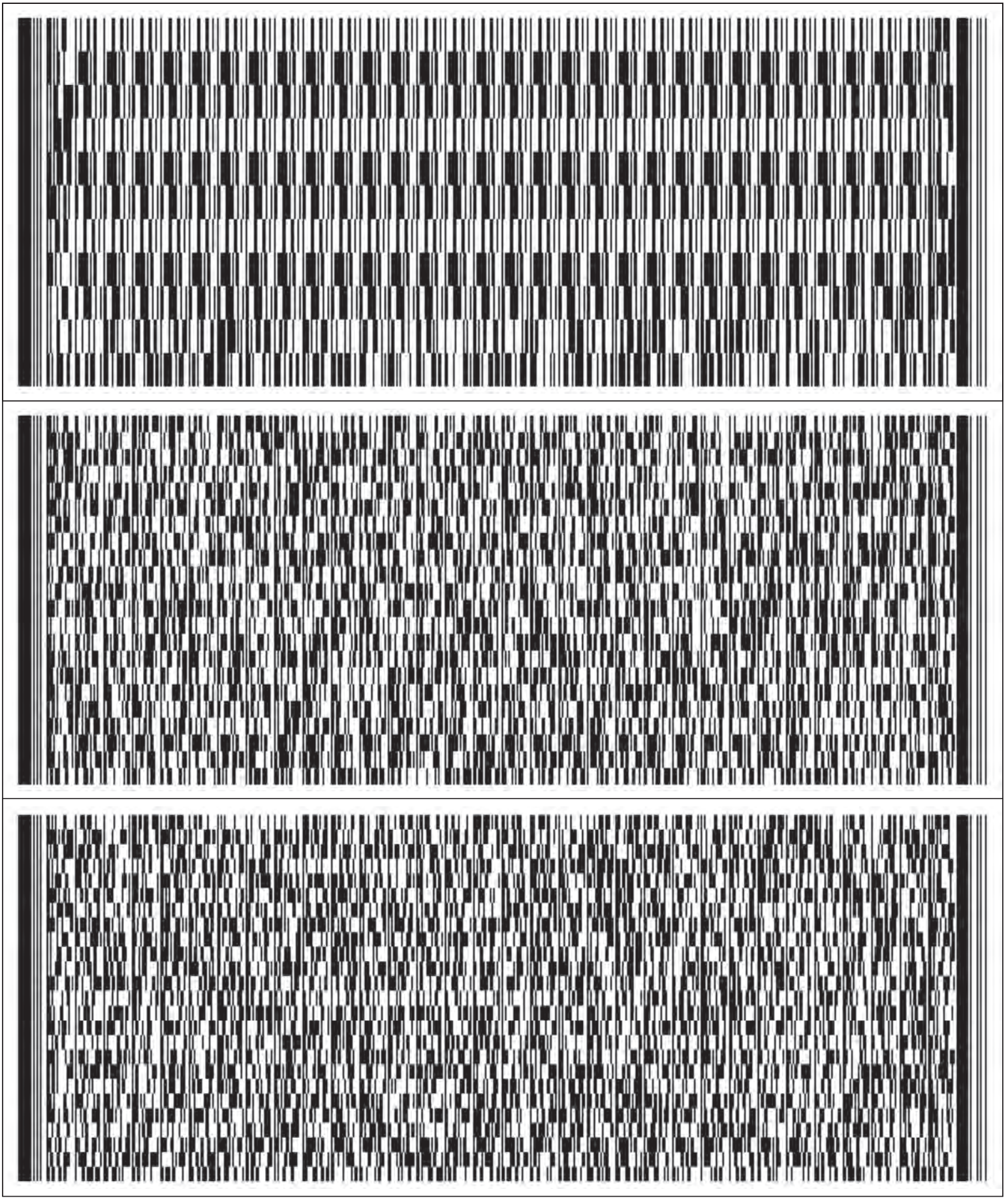
The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information 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.

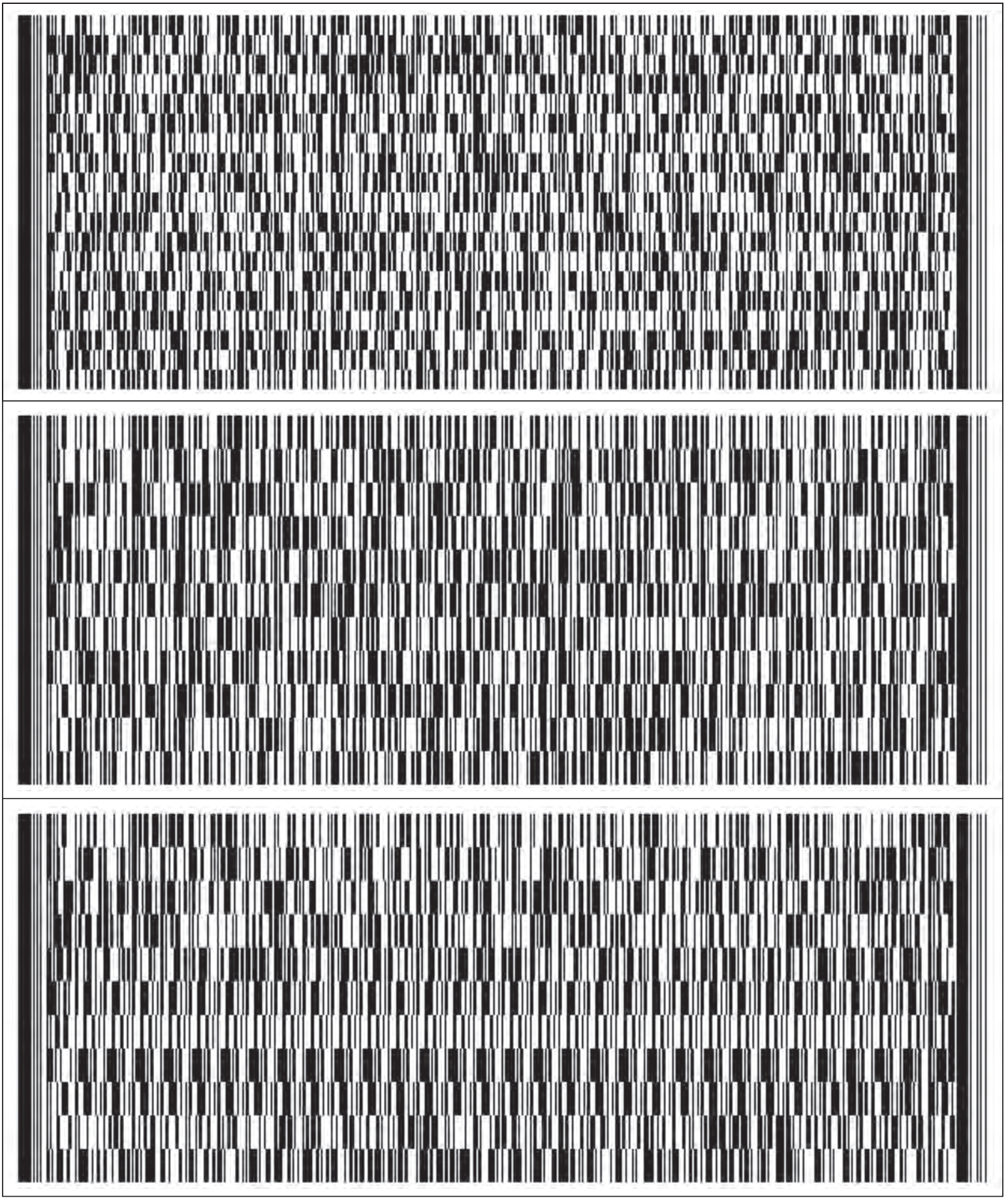
3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
	Steve Steinborn	11/06/2019

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)
	Appendix A. Analytical Data from Representative Batches of CITREM	Submission
	Appendix B. Controls for Potential Contaminants	Submission
	Appendix C. Toxicological Studies on Esters Structurally Similar to CITREM	Submission
	Appendix D. PubMed Literature Searches	Submission





GRAS Conclusion for the Use of Citric Acid Esters of Mono- and Diglycerides (CITREM) in Exempt Infant Formula for Term Infants

SUBMITTED BY:

Hogan Lovells US LLP
555 13th St NW
Washington, DC 20004

SUBMITTED TO:

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

CONTACT FOR TECHNICAL OR OTHER INFORMATION:

Hogan Lovells US LLP
555 13th St NW
Washington, DC 20004

November 7, 2019

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List of Acronyms

ADI	acceptable daily intake
bw	body weight
CCFAS	Codex Compendium of Food Additive Specifications
CFR	Code of Federal Regulations
CFU	colony forming unit
cGMP	current Good Manufacturing Practice
CITREM	citric acid esters of mono- and diglycerides
d	day
EDI	Estimated Daily Intake
EU	European Union
F	female
FAO	Food and Agriculture Organization of the United Nations
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
FSANZ	Food Standards Australia New Zealand
g	gram
GCFE	glycerol citrate fatty acid esters
GLP	glycerol lactopalmitate
GMP	good manufacturing practice
GRAS	Generally Recognized As Safe
GRN	GRAS Notice
h	hour
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kcal	kilocalorie
kg	kilogram
M	male
mg	milligram
mL	milliliter
n	number
ND	not detected
NMT	not more than
PAH	polycyclic aromatic hydrocarbons
PCBs	polychlorinated biphenyls
PICU	pediatric intensive care unit
ppm	parts per million
SCF	Scientific Committee on Food

TCA	tricarboxylic acid cycle
U.S.	United States
WHF	whey hydrolysate formula
WHO	World Health Organization
wk	week
y	year

Part 1: Signed Statements and Certification

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

Name and Address of Notifier

Hogan Lovells US LLP

555 13th St NW

Washington, DC 20004

Name of GRAS Substance

The substance that is the subject of this GRAS notice is citric acid esters of mono- and diglycerides, commonly referred to as CITREM. Throughout this notification, the substance is referred to as CITREM.

Intended Use and Consumer Exposure

The proposed use of CITREM is as an emulsifier at a maximum level of 233 mg per 100 mL (2330 mg per L or 0.233%) in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction.

Basis for Conclusion of GRAS Status

Hogan Lovells US LLP's conclusion of GRAS status for the intended use of CITREM is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

Pre-Market Approval Exclusion Claim

Use of CITREM is not subject to the pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Hogan Lovells US LLP has concluded that such use is GRAS through scientific procedures.

Availability of Information

The data and information that serve as the basis for this GRAS conclusion, as well as the information that has become available since the GRAS conclusion, will be sent to the FDA upon request, or are available for the FDA's review and copying during customary business hours at the office of Hogan Lovells US LLP.

Exemptions from Disclosure

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

Certification Statement

On behalf of Hogan Lovells US LLP, I hereby certify that, to the best of my knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, known to me and pertinent to the evaluation of the safety and GRAS status of the use of the substance.

11/07/2019

_____ _____

Name Steven B. Steinborn Date

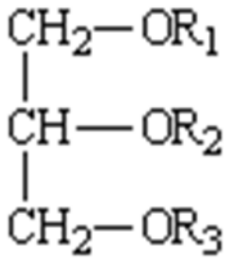
Part 2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

Identity

The substance that is the subject of this GRAS review is CITREM, which is a common name for citric acid esters of mono- and diglycerides of fatty acids. Other names for the subject of this GRAS review include citroglycerides, mono- and diglycerides of fatty acids esterified with citric acid, citric acid ester of glyceryl monooleate, citric and fatty acid esters of glycerol, citroglycerides, mixed esters of citric and edible fatty acids with glycerol, monoglyceride citrate, and CAEM. In the Codex Alimentarius General Standards for Food Additives, citric and fatty acid esters of glycerol is designated as E472c and INS 472c.

CITREM is an oil to waxy material, white to ivory in color. In CITREM, at least one of R1, R2, or R3 represents a citric acid moiety, one represents a fatty acid moiety, and the remaining moieties may represent citric acid, a fatty acid, or hydrogen as defined by JECFA (2016). Fatty acid moieties commonly have a chain length from C12 to C22. The general structural formula of CITREM is presented in Figure 1 below.

Figure 1. Structural formula of CITREM

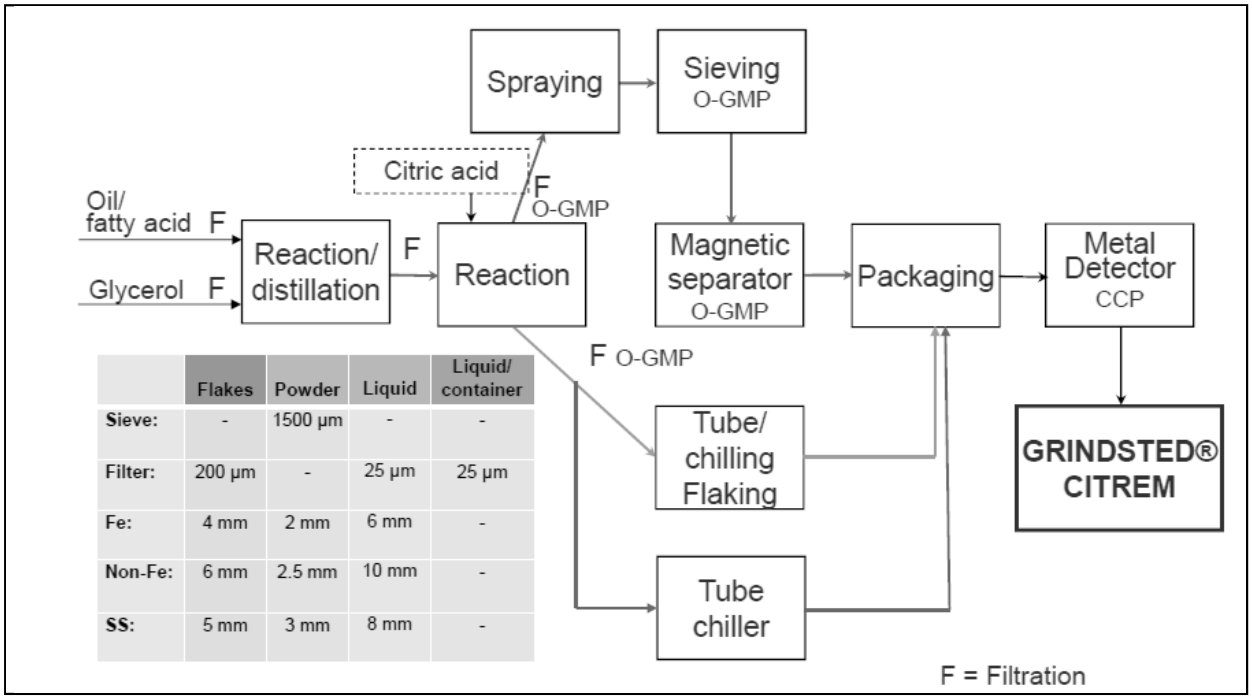


At least one of R1, R2, R3 represents a citric acid moiety, one represents a fatty acid moiety, and the remainder may represent citric acid, fatty acid, or hydrogen (JECFA 2016).

Method of Manufacture

CITREM is produced by reacting citric acid with mono- and diglycerides of fatty acids produced from glycerol and fully hydrogenated palm oil. During production, the product is partially neutralized with sodium-acetate. The product is spray-cooled into a coarse powder and packaged. The production of CITREM is conducted in accordance with current Good Manufacturing Practice (cGMP). A flow diagram of the production process is provided in Figure 2.

Figure 2. Flow Diagram for Production of CITREM



All ingredients used in the production of CITREM are food-grade materials, namely fully refined, hydrogenated, edible palm oil which consists primarily of palmitic acid and stearic acid, both of which are saturated fatty acids; glycerol (complies with food additive E422); citric acid (complies with food additive E330); and sodium-acetate (complies with food additive E262(i)).

Specifications

Specifications for the CITREM that is the subject of this GRAS determination and methods of analysis for parameters included in the specifications are presented in Table 1.

Table 1. Specifications and Methods of Analysis for CITREM

Parameter	Specification	Method of Analysis
Total citric acid, %	13-50	CCFAS: Monograph 19 (2016)
Total glycerol, %	8-33	CCFAS: Monograph 19 (2016)
Free glycerol, %	NMT 2	FAO JECFA Monograph, vol. 4, p. 173
Total fatty acids (as oleic acid), %	37-81	CCFAS: Monograph 19 (2016)
Sulfated ash (800 ± 25°C), %	NMT 10	FAO JECFA Monograph, vol. 4, p. 54
Acids other than citric and fatty, %	<1	GC-method; Samples containing 1 % of the unwanted acids are used as references for the limit testing
Acid value, (mg KOH/g)	10-25	FAO JECFA Monograph, vol. 4, p. 161

Saponification value, (mg KOH/g)	220-250	FCC, 11th Ed., p. 408
Lead, mg/kg	NMT 2	ISO-17294m
Cadmium, mg/kg	NMT 1	ISO-17294m
Arsenic, mg/kg	NMT 1.5	ISO-17294m
Mercury, mg/kg	NMT 1	ISO-17294m
Salmonella	absent in 1 g	ISO 6579-1
Enterobacteria	absent in 1 g	ISO 21528-1
Total plate count, CFU/g	Max 5000	3M Aerobic Count Petrifilm Plate 3M 01/01-09/89
Yeast and mold, CFU/g	Max 100	3M Yeast & Mold Petrifilm Plate 3M 01/13-07/14
Abbreviations: CCFAS – Codex Compendium of Food Additive Specifications; CFU – colony-forming units; FAO – Food and Agriculture Organization; FCC – Food Chemicals Codex; GC – gas chromatography; JECFA – Joint Expert Committee on Food Additives; ISO – International Organization for Standardization; NMT – not more than		

Table 2 presents the specifications along with specifications established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Union (EU), the Food Chemicals Codex (FCC), and a manufacturer of infant formula that determined use of CITREM to be GRAS for use in exempt amino acid-based and extensively hydrolyzed infant formulas as specified in GRN 511.

The referenced CITREM specifications consistently identify a minimum concentration of citric acid (13%), limits on free glycerol, and heavy metals. Specifications for the CITREM that is the subject of this GRAS conclusion also include limits for free fatty acids other than citric acid and fatty acids, saponification value, and potential microbiological contaminants.

Table 2. Comparison of Referenced CITREM Specifications

Parameter	JECFA 2016	EU 2008, EU 2012	GRN 511	FCC 11	Current GRAS
Total citric acid, %	13-50	13-50	13-50	13-50	13-50
Total glycerol, %	8-33	8-33	8-33	8-33	8-33
Free glycerol, %	NMT 4	NMT 2	NMT 2	NMT 4	NMT 2
Total fatty acids (as oleic acid), %	37-81	-	37-81	37-81	37-81
Sulfated ash[a] (800±25°C), %	NMT 10	NMT 10	NMT 10	NMT 10	NMT 10
Acids other than citric and fatty, %	-	<1	-	-	<1
Acid value, (mg KOH/g)	-	NMT 130	20-40	-	10-25
Saponification value, (mg KOH/g)	-	-	245-275	-	220-250
Lead, mg/kg	NMT 2 [b]	NMT 2	NMT 1.5	NMT 2	NMT 2
Cadmium, mg/kg	-	-	NMT 0.1	-	NMT 1
Arsenic, mg/kg	-	-	NMT 0.2	-	NMT 1.5
Mercury, mg/kg	-	-	NMT 0.1	-	NMT 1
Salmonella	-	-	ND in 25 g	-	absent in 1 g
Enterobacteria	-	-	NMT 10	-	absent in 1 g
Total plate count, CFU/g	-	-	-	-	Max 5000
Yeast and mold, CFU/g	-	-	-	-	Max 100

Parameter	JECFA 2016	EU 2008, EU 2012	GRN 511	FCC 11	Current GRAS
CFU – colony-forming units; ND – not detected; NMT – not more than [a] NMT 0.5% for non-neutralized products, NMT 10% for partially or wholly neutralized products. [b] Specification for use in foods for the general population.					

Results from analyses of representative non-consecutive lots of CITREM demonstrate that the product consistently meets these specifications (Table 3 and Appendix A). The analytical data also demonstrate that the typical concentration of total citric acid in CITREM is 15%, which is well below the maximum concentration of 50%.

Table 3. Comparison of Referenced CITREM Specifications

Parameter	Specification	Batch 4012692136	Batch 4012465697	Batch 4013014634
Total citric acid, %	13-50	15	15	15
Total glycerol, %	8-33	25	23	24
Free glycerol, %	NMT 2	1.1	0.8	0.9
Total fatty acids (as oleic acid), %	37-81	- - [a]	- -	- -
Sulfated ash[a] (800±25°C), %	NMT 10	2.3	2.2	2.3
Acids other than citric and fatty, %	<1	Pass	Pass	Pass
Acid value, (mg KOH/g)	10-25	14	14	9
Saponification value, (mg KOH/g)	220-250	240	240	240
Lead, mg/kg	NMT 2	0.4	0.8	0.4
Cadmium, mg/kg	NMT 1	0.1	0.2	0.1
Arsenic, mg/kg	NMT 1.5	1.0	1.0	0.5
Mercury, mg/kg	NMT 1	0.1	0.1	0.1
Salmonella	absent in 1 g	Pass	Pass	Pass
Enterobacteria	absent in 1 g	Pass	Pass	Pass
Total plate count, CFU/g	Max 5000	100	100	100
Yeast and mold, CFU/g	Max 100	10	10	10
CFU – colony-forming units; NMT – not more than [a] Controlled via raw materials to be within specifications.				

In addition to the specifications listed in Table 1, controls on raw materials used to produce CITREM ensure the final product meets specified limits for iodine value, pH and dropping point. Ingredient specifications also are in place to ensure that CITREM meets established residues for potential contaminants of concern including polycyclic aromatic hydrocarbons (PAH), dioxins (PCDD + PCDF), dioxin-like PCBs, non dioxin-like PCBs and pesticides (Appendix B).

Technical Effect

The intended technical effect of CITREM in calorically-dense, exempt infant formula is that of an emulsifier or emulsifying salt as detailed in 21 CFR §170(o)(3). A calorically dense formula requires robust emulsification to ensure that the formula remains stable over its shelf life to minimize the risk of fat separation and sedimentation of insoluble particles. Stability of the emulsion is also important to maintain acceptable sensory aspects of appearance, color, odor,

taste, and mouthfeel. Product acceptance and palatability are especially important for older infants (over 6 months) requiring the use of a calorically dense formula.

Part 3. Dietary Exposure

Proposed Use and Level

The proposed maximum use of CITREM is 233 mg CITREM per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction. Calorically dense infant formula provides 100 kcal 100 mL while standard infant formulas and human milk typically provide 67 kcal per 100 mL and 65 kcal per 100 mL, respectively (Green Corkins and Shurley, 2016; IOM, 2005).

Estimated Daily Intakes

Formula Intake

The daily intake of CITREM from the proposed use in calorically dense formula was estimated assuming (1) a maximum use of 233 mg CITREM per 100 mL, (2) an energy density of 100 kcal per 100 mL in the infant formula, and (3) formula intake representative of intakes among the population of term infants requiring a calorically dense infant formula and/or fluid restriction.

Formula intake among populations of term infants administered calorically dense infant formula has been examined in clinical trials and in a retrospective study of infants in the pediatric intensive care unit (PICU). These data can be used to estimate intake of CITREM from the proposed use in calorically dense infant formula.

As summarized in Table 4, the target intake of calorically dense formula, as documented in the identified published literature, ranges from 130 kcal per kilogram bodyweight per day (kcal/kg bw/day) while in the intensive care unit to 200 kcal/kg bw/day over longer periods of intake (i.e., 3-6 weeks). Target daily formula intakes in interventions spanning multiple weeks were based on estimated energy needs on a per kg bw basis with stress factors to support catch-up growth, such as the factors of 1.5 to 2.0 times basal metabolic needs as recommended in the Schofield equations (e.g., Clarke et al., 2007; Eveleens et al., 2018).

Reported intake of formula by infants in the identified clinical studies was consistently lower than the targeted intake. Among the two 5-day interventions, mean formula intake was 119 kcal/kg bw/day in one study and between 55 to 120 kcal/kg bw/day in the second (Cui et al., 2017; de Betue et al., 2011). In the retrospective study, mean formula intake was reported at 105 kcal/kg bw/day (Eveleens et al., 2018), which is consistent with daily formula intake at baseline in an unpublished study (INGROTO, 2012). Based on these four studies, intake of formula at a level of 120 kcal/kg bw/day provides a conservative estimate of typical intake. This estimate of intake is consistent with reference energy needs of 113 to 123 kcal/kg bw/day for catch-up growth in children assuming a rate of gain of 10 g/kg bw/day (IOM, 2005; Table 5-32).

Calorically dense term infant formulas provide 100 kcal per 100 mL; therefore, 120 kcal/kg bw/day is equivalent to 120 mL/kg bw/day of formula.

The 6-week intervention reported higher intakes, with a median formula intake of 140 kcal/kg bw/day and intakes ranging from 103 to 175 kcal/kg bw/day (Clarke et al., 2007). The highest achieved formula intake of 175 kcal/kg bw per 24 h in the 6-week intervention provides a conservative estimate for evaluating high infant formula intake and in turn, constituents in the formula. With a caloric density of 100 kcal per 100 mL, intake of 175 kcal/kg bw/day is equivalent to 175 mL/kg bw/day of formula.

Table 4. Formula Intake in Studies of Term Infants Consuming a Calorically Dense Infant Formula

Study	Study Population; Number of infants on test formula; Duration of Intervention	Age (mean ± SD) / Bodyweight (bw) at Baseline	Target Daily Formula Intake	Reported Daily Formula Intake
de Betue et al., 2011 (also van Waardenburg et al., 2009)	Infants admitted to the pediatric intensive care unit with respiratory failure due to viral bronchiolitis n = 8; 5 days	age: 2.7 ± 1.4 months bw: 3.97 ± 0.94 kg	130 kcal/kg bw/day	Mean reported intake (day 5): 119±25 kcal/kg bw/day Range of intake: 105-147% of recommended intake for energy (as cited by Butte 2005)
Clarke et al., 2007	Infants with faltering growth due to cardiac lesions, cystic fibrosis, or other causes n = 26; 6 weeks	age: 5.6 (2.4 - 31.0) months (median, range) bw: Not reported (5.4 g fat per 100 kcal = 49.5% energy from fat)	150-200 kcal/kg bw/day (based on Schofield equation with factors for catch up growth)	Median: 140 kcal/kg bw/day Range of intake: 103-175 kcal/kg bw/day
Cui et al., 2017	Infants admitted to cardiac intensive care unit after congenital heart surgery n = 26; 5 days	age: 4.69 ± 3.54 months bw: 5.24 ± 1.66 kg	130 kcal/kg bw/day	Range of intake: 55-120 kcal/kg bw/day
Eveleens et al., 2018	Retrospective study of infants admitted to a pediatric intensive care unit n = 76; 30 (21-54) days on formula (median, interquartile	age: 76 (30-182) days bw: 3.94 (3.29-5.80) kg (median, interquartile range)	2 x calculated resting energy requirement (based on Schofield equation for weight)	Mean reported intake: 104.6 ± 19.4 kcal/kg bw/day

Study	Study Population; Number of infants on test formula; Duration of Intervention	Age (mean ± SD) / Bodyweight (bw) at Baseline	Target Daily Formula Intake	Reported Daily Formula Intake
	range)			
INGROTO, 2012	Infants requiring calorically dense formula, including: congenital heart disease, chronic lung disease, non-organic failure to thrive, or other conditions n = 14; 12 weeks	age: 19.7 ± 8.2 weeks at screening bw: 4.29 ± 1.04 kg at baseline	No target intake recommendation; intake was based on clinical practice.	105 kcal/kg bw/day at baseline

Based on data in these clinical studies, the estimated daily intake of calorically dense infant formula for the average or typical infant therefore is assumed to be 120 kcal/kg bw/day, while the estimated daily intake of calorically dense infant formula for an infant representative of a high consumer is assumed to be 175 kcal/kg bw/day. The estimate of typical intake of the calorically dense formula (120 kcal/kg bw/day) in this assessment is consistent with mean formula intake for formula-fed infants with the highest intake per kg bw as reported by Fomon (1993), namely 121.1 kcal/kg bw/day for boys age 14-27 days. Fomon reported a 90th percentile formula intake by this male population of 141.3 kcal/kg bw/day. The estimate of high intake of the calorically dense formula of 175 kcal/kg bw/day exceeds a conservatively high average intake among healthy infants by a factor of up to 1.5 (175 kcal/kg bw/day vs 120 - 140 kcal/kg bw/day), which is a reflection of the higher energy needs of the target population.

CITREM Intake

Assuming the proposed maximum use of CITREM of 233 mg per 100 mL, a conservative EDI of CITREM is 408 mg/kg bw/day based on intake of 175 kcal/kg bw/day, which is representative of a high infant formula intake in the target population. Assuming typical formula intake of 120 kcal/kg bw/day, the EDI of CITREM is 280 mg/kg bw/day (Table 5).

Citric Acid Intake

CITREM is a source of citric acid, with each 100 g of CITREM typically providing 15 g citric acid and up to 50 g citric acid per the product specifications. The estimated CITREM intake of 408 mg/kg bw/day (based on a high formula intake of 175 kcal/kg bw/day) therefore provides 61 mg or 204 mg citric acid per kg bw/day assuming typical and maximum concentrations of citric acid in CITREM, respectively. Analysis of various infant formulas in the marketplace has shown that products provide on average 64 mg citrate per 100 mL based on a mean concentration of 3.34 mmol/L citrate and a molecular weight of 192.124 g/L for citric acid (FAO/WHO 2015; Hoppe et al., 1998). Infant formula consumed at a level of 175 mL/kg bw/day therefore provides an estimated 112 mg citric acid per kg bw/day in addition to citric acid from CITREM. The total

estimated intake of citric acid from formula, including citric acid from the proposed maximum use of CITREM and citric acid from other ingredients typical in infant formula, is 173 mg citric acid per kg bw/day assuming the typical concentration of citric acid in CITREM. Assuming the maximum permitted concentration of citric acid in CITREM (i.e., 50%), total intake of citric acid is estimated at 316 mg citric acid per kg bw/day. Based on a typical formula intake of 120 kcal/kg bw/day and assuming the maximum permitted concentration of citric acid in CITREM (i.e., 50%), total intake of citric acid is estimated at 217 mg citric acid per kg bw/day (Table 5).

Table 5. Estimated Intake of CITREM and Citric Acid from the Maximum Proposed Use of CITREM

Energy Dense Formula[a]		CITREM (mg/kg bw/day)	Citric Acid (mg/kg bw/day)				
Intake	kcal/kg bw/day	Maximum of 233 mg/100 mL	Typical from CITREM (15%)	Maximum from CITREM (50%)	Back-ground from formula[b]	Typical TOTAL	Maximum TOTAL
Typical	120	280	42	140	77	119	217
High	175	408	61	204	112	173	316

[a]Assume 100 kcal per 100 mL

[b] 64 mg citric acid per 100 mL in infant formula based on a mean concentration of 3.34 mmol/L citrate and a molecular weight of 192.124 g/L for citric acid (FAO/WHO 2015; Hoppe et al., 1998).

Part 4. Self-Limiting Levels of Use

Citric acid esters of mono- and diglycerides (CITREM) is intended for use as an emulsifier at a maximum level of 233 mg per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction. We are not aware of technological or palatability issues associated with the proposed use levels. Self-limiting levels of use are not applicable to this notice.

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

The conclusion of GRAS status of the use of CITREM in exempt infant formula for term infants was based upon scientific procedures. Experience based on common use in food before 1958 is not applicable to this notice.

Part 6. Narrative

Introduction

CITREM is a mixture of citric acid esters and fatty acid esters. The citric acid esters are similar in structure to triglycerides, with the exception of at least one citric acid moiety substituted for a fatty acid moiety while the fatty acid esters in CITREM bear structural similarity to naturally occurring triglycerides found in food.

The safety of the use of CITREM, including use in infant formula, has been comprehensively evaluated by authoritative bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Union's Scientific Committee on Food (SCF), Food Standards Australia New Zealand (FSANZ), and Health Canada. In the U.S., the use of the identical concentration of CITREM (233 mg per 100 mL) in amino-acid based and extensively hydrolyzed infant formulas was determined to be GRAS and favorably reviewed by FDA (FDA 2014). The intended use level of CITREM in this GRAS evaluation is identical to a recognized safe use of the ingredient and differs only in the type of infant formula to which the ingredient would be added. At a given time, infants typically consume only one type of formula matched to their nutritional needs, therefore the proposed use would not increase the amount of CITREM consumed by an infant from infant formula.

The safety of the use of CITREM in infant formula has been established through consideration of the biochemical nature of the substance and the toxicity of the substance, which is intrinsically low. The potential for citric acid to cause adverse effects on tolerance, namely diarrhea, also was considered. The data and information on which the safety of the proposed use of CITREM in exempt infant formula for term infants can be established are summarized below.

Permitted Uses

Citric acid esters of mono- and diglycerides (CITREM) is permitted for use as an additive in foods, including use specifically in infant formula. Permitted uses of CITREM in the U.S. are summarized below, as are recognized uses outside the U.S. for use of CITREM in infant formulas.

Uses of CITREM in the United States

CITREM is included in the U.S. FDA's Substances Added to Food (formerly EAFUS, i.e., Everything Added to Food in the United States) under the name mono- and diglycerides, citric acid esters and sodium and calcium salts (reference number 977093-28-9).

Citric acid esters of mono- and diglycerides (CITREM) was determined to be GRAS for use as an antioxidant, emulsifier, stabilizer, and thickener in exempt amino acid-based and extensively hydrolyzed infant formulas at a maximum level of 233 mg per 100 mL of formula (as

consumed). This GRAS determination was filed as GRN 511 (Nestle Nutrition U.S., 2014), and FDA responded with a letter indicating the agency had no concerns about the GRAS conclusion under the intended conditions of use (Keefe, 2014).

Citric acid esters of mono- and diglycerides (referred to as citroglycerides, which is another name for CITREM) also were determined to be GRAS for use as an emulsifier in combination with lauramide ethyl ester in food in general, including meat and poultry, as detailed in GRN 222 (LAMIRSA, 2007). The uses include use in carbonated beverages at levels up to 563 milligrams per kilogram (mg/kg) and certain other food categories, including meat and poultry products, at levels up to 1125 mg/kg. The FDA responded to this notification with a letter indicating the agency had no concerns about the GRAS conclusion under the intended conditions of use (Tarantino, 2007).

Monoglyceride citrate, defined as a mixture of glyceryl monooleate and its citric acid monoester, belongs to the group of citric acid esters of mono- and diglycerides. Monoglyceride citrate with a total citric acid (free and combined) content of 14-17% is a food additive permitted for direct addition to food which may be used in antioxidant formulations added to oils and fats at a level that does not exceed 200 ppm of the combined weight of the oil or fat and the additive (21 CFR §172.832).

Uses of CITREM in Infant Formula outside the United States

The CODEX Standard for Infant Formula, CODEX STAN 72-1981, identifies CITREM as a food additive (an emulsifier) acceptable for use in the preparation of infant formula, at a maximum level of 900 mg per 100 mL (as consumed) in all types of liquid infant formula, follow-up formula, and formula for special medical purposes, and a maximum level of 750 mg per 100 mL (as consumed) in all types of powder infant formula, follow-up formula, and formula for special medical purposes.

CITREM is an approved additive for use in infant formula in many jurisdictions outside the U.S., including the European Union, Canada, Australia/New Zealand, and other countries; permitted uses are summarized in Table 6 below.

Table 6. Permitted Uses of CITREM in Infant Formula in the United States and Globally

Authoritative Body	Permitted Use	Reference
United States	Up to 233 mg per 100 mL in exempt amino acid-based and extensively hydrolyzed infant formulas	GRN 511
CODEX	Up to 900 mg per 100 mL (as consumed) in liquid infant formula, follow-up formula, and formula for special medical purposes	CODEX STAN 72 – 1981
	Up to 750 per 100 mL (as consumed) in powdered infant formula, follow-up formula, and formula for special medical purposes	
European Union	Up to 750 mg per 100 mL in infant formula and follow-on formula when sold as dry powder	Commission Regulation

Authoritative Body	Permitted Use	Reference
	Up to 900 mg per 100 mL in infant formula and follow-on formula sold as liquid where the products contain partially hydrolyzed proteins, peptides or amino acids	(EU) No 1129/2011 (2011)
Canada	Up to 155 mg per 100 mL in infant formula based on crystalline amino acids or protein hydrolysates, or both, as an emulsifier	Minister of Justice, 2018
Switzerland, Turkey, Mexico, Russia, Brazil, China	CITREM is permitted in infant formula, follow-on formula, and infant foods for special medical purposes	As cited in FAO 2015
Other countries, e.g., Chile, Singapore, Saudi Arabia, other countries in the Middle East	Permission to commercialize formulas for infants and young children with INS 472c	

Previous Reviews of the Safety of Use of CITREM in Infant Formula

Introduction

CITREM has been the subject of numerous safety evaluations including JECFA, the SCF (1998, 2002), and Health Canada (2010) that resulted in permitted uses of CITREM in infant formula as summarized above. JECFA's first evaluation of CITREM and related compounds (i.e., glycerol esters of acetic acid, lactic acid, and tartaric acid) resulted in allocation of an acceptable daily intake (ADI) for CITREM of "not specified" (FAO 1967; WHO 1974). This JECFA evaluation was based on biochemical and metabolic studies showing that the substance is completely hydrolyzed in the gastrointestinal tract to normal constituents of the diet, and an understanding of basic metabolism and lack of toxicity of citric acid, glycerol, and fatty acids of glycerol.

The conclusion of GRAS status of use of 233 mg CITREM per 100 mL in exempt amino acid-based and extensively hydrolyzed infant formulas also was based on evaluation of the biochemical characteristics of CITREM and related substances. The assessment of safety presented in GRN 511 included a review of evidence as summarized by JECFA as well as newer *in vitro* evidence on the hydrolysis of organic esters of mono- and diglycerides. Collectively, the evidence supported a conclusion that CITREM is metabolized and utilized in a manner similar to that of triglycerides, and the intended use of CITREM is safe and GRAS. FDA was notified of this GRAS conclusion and responded with a letter stating there were no concerns (FDA 2014).

Shortly after use of CITREM was concluded to be GRAS in exempt amino acid-based and extensively hydrolyzed infant formulas, JECFA completed a comprehensive evaluation of the safety of use of CITREM at levels above typical intake defined as 270 mg per 100 mL (FAO 2015). The review considered biochemical aspects of CITREM, available toxicity data, clinical evidence in infants for CITREM and its hydrolysis products, and dietary exposure to CITREM and citric acid (FAO 2015) and was based on information on CITREM and other structurally

related compounds as well as information identified in searches of the scientific literature between 1973 (i.e., the time of the earlier JECFA review) through April 2014. Typical use of CITREM in the evaluation corresponded to an estimated CITREM intake of 599 mg/kg bw/day and a citrate intake of 442 mg/kg bw/day for very young male infants at the 95th percentile of energy intake. At a typical level of intake, diarrhea was concluded to be unlikely given the available evidence and therefore presents no safety concerns. Higher levels of CITREM also were concluded to present no safety concerns.

The key evidence considered by JECFA in the early safety assessment of CITREM (FAO 1967; WHO 1974) as well as evidence considered in the more recent JECFA review and evidence considered in the GRAS conclusion summarized in GRN 511 is summarized below.

Biochemical Characteristics of CITREM and Related Compounds

As part of comprehensive safety evaluations of CITREM, the metabolic fate of CITREM including absorption, distribution, and excretion were reviewed. The fate of other organic acid esters of glycerol that share similar biochemical characteristics, namely acetic, lactic and tartaric acid esters, also was considered.

Absorption, Distribution and Excretion of CITREM

CITREM is not considered to be absorbed intact, rather it is hydrolyzed in the digestive tract into its component parts of citric acid (or related organic acid), free fatty acids, and glycerol. The first JECFA review of the biochemical aspects of CITREM included evaluation of digestibility in *in vitro* and *in vivo* studies. As reported by JECFA, Lang (1964, as cited by FAO 1967) demonstrated a similar extent of digestion of CITREM *in vitro* using pancreatic lipase and liver esterase as observed with spontaneous hydrolysis at pH 7.5 to 8.5. In a study completed by the Huntingdon Research Center and reviewed by JECFA (Huntingdon 1966, as cited by FAO 1967), groups of 20 male and female rats on a calorie-restricted diet were examined for 10 days while consuming the CITREM compound or a physical mixture of its constituents at 23.1 or 37.5% in the diet, or isocaloric diets with 16.7 or 35.5% lard. Digestibility of the ester and the unesterified compounds did not differ based on estimates of fecal fat and body distributions of fatty acids. In another study reviewed by JECFA, food intake and body weight did not differ between two groups of 5 male and 5 female weanling rats fed diets containing 0 or 20% CITREM, while digestibility of CITREM was calculated to be 99% (Rosner 1959, as cited by FAO 1967).

As part of JECFA's more recent review of CITREM, JECFA examined a 2014 study that investigated the digestion of CITREM and infant formulas containing CITREM through an *in vitro* two-phase model with varied pH and bile salt concentrations to mimic the preterm and term infant stomach and duodenum (Amara et al., 2014). The commercial CITREM used in this study was composed of 65.5% fatty acid esters and 34.5% glycerol citrate fatty acid esters (GCFE). The objectives of the study were: (1) to identify enzymes that may be involved in the hydrolysis of CITREM, (2) to quantify CITREM hydrolysis using an *in vitro* model of digestion representative of the human infant, and (3) in the same *in vitro* model, to determine the impact of CITREM on fat digestion in CITREM-containing infant formula.

The digestibility of CITREM was carried out with individual enzymes including recombinant dog gastric lipase (which is similar to human gastric lipase), recombinant human pancreatic lipase, recombinant pancreatic lipase-related protein 2, native porcine pancreatic lipase, human pancreatic carboxyl ester hydrolase, and porcine pancreatic extract to mimic human pancreatic juice. Maximal lipase activity occurred at a CITREM concentration of 900 mg/100 mL, corresponding to the maximum concentration of CITREM present in commercial liquid formulas for special medical purposes. CITREM at a concentration of 900 mg/100 mL and a lower concentration of 300 mg/100 mL, often used in other infant formulas, were employed in the subsequent *in vitro* infant digestion. All lipases were active in hydrolyzing CITREM. Gastric lipase was active at low pH and in the presence of bile salts, indicating potential activity in both the stomach and intestines. Pancreatic lipase activity was observed in the presence and absence of bile salts, suggesting that the enzyme functions in both term and preterm infants (Amara et al., 2014).

In the two-phase *in vitro* model of digestion in term and preterm infants, CITREM was incubated with gastric lipase for 30 minutes and then with pancreatic lipase and bile salts for 60 minutes. At 90 minutes, hydrolysis was maximal for CITREM (ranging from 14.6% to 24.3%) and CITREM-containing infant formula (17% in preterm infants and 28% in term infants). Approximately one-quarter of the esters were hydrolyzed in both CITREM and CITREM-containing infant formula, though in the CITREM-infant formula mixture it was not possible to distinguish between hydrolysis of fatty acid esters from CITREM or the infant formula. Nearly identical levels of hydrolysis (approximately 29%) were obtained for fat alone and CITREM-stabilized fat emulsions, showing that the presence of CITREM does not alter fat digestion. Hydrolysis of pure GCFE ranged from 47% to 58%. Nuclear magnetic resonance imaging revealed that, while pure GCFE was completely hydrolyzed during digestion, 20 to 30% of CITREM remained undigested at 90 minutes, suggesting an effect of other glycerides. Additionally, it was demonstrated that fatty acids of GCFE in CITREM were released as glycerides or free fatty acids, but the resulting glycerol citric acid esters were not completely hydrolyzed into glycerol and citric acid (Amara et al., 2014).

Results from this study indicate that CITREM was not completely hydrolyzed into its component parts as initially expected, with predominantly the glycerol citric acid esters resisting digestion in this *in vitro* model. Additionally, the digestion model did not include lingual lipase, which is active in infants. As the digestion in this study simulated only the upper gastrointestinal tract, it is possible that further digestion of CITREM and glycerol citric acid esters occurs in the infant jejunum and beyond as free fatty acids and glycerides from the breakdown of fats form micelles and are absorbed by the enterocytes.

Based on the available evidence, the JECFA committee concluded that *in vivo* CITREM is likely to be substantially, though not entirely, hydrolyzed, and that any remaining partially hydrolyzed products, for example glycerol citric acid esters, would not present a safety concern.

Biochemical Characteristics of Related Substances

Data on the absorption, distribution and excretion of the component compounds of acetic acid esters and lactic acid esters provides surrogate evidence for the handling of citric acid esters.

As reported by JECFA (1967), Ambrose & Robbins (1956b) carried out a feeding study in rats to determine the absorption of acetoglycerides using diets containing 20% acetic acid esterified to either saturated or unsaturated fatty acids. Control groups received a fat free diet or a diet with 20% vegetable shortening. Absorption of unsaturated acetoglycerides (acetooleins) was better compared to absorption of saturated acetoglycerides (acetostearins), with overall digestibility coefficients of 94 to 99% (Ambrose & Robbins, 1956b). Additionally, Coleman and colleagues (1963) found no differences in tissue cholesterol levels (plasma, liver, nor adrenals) in male weanling rats fed diets containing 0 or 30% acetostearins for 20 weeks.

In the review of lactic acid esters, JECFA notes that common components of lactic acid esters of mono- and diglycerides are glycerol lactopalmitate (GLP) and lactostearate. Treon and colleagues (1962) reported findings of a study on GLP. The investigators reported rapid production of glycerol, lactic acid and palmitic acid in an *in vitro* study of GLP hydrolysis in the presence of hog pancreatic lipase, and in a study in rats, the lactate moiety of GLP was found to be metabolized at the same rate and in a similar manner to free lactic acid. The lactic acid metabolite was largely absorbed, distributed randomly throughout tissues in the body, and readily stored and oxidized by the liver (Treon et al., 1962). McKennis and colleagues (1958) also reported findings of studies on GLP; the investigators observed hydrolysis of ^{14}C-labeled GLP and absorption of its component parts in gavaged dogs as demonstrated by the appearance of lactic acid in the thoracic duct lymph and blood. Metabolism of GLP components was confirmed with 50% of the administered dose expired as labeled CO_2 over 48 hours.

Toxicological Data on CITREM and Related Compounds

Toxicological data on CITREM are limited, and include studies on genotoxicity, short-term studies, and studies of the effects of fat absorption.

Genotoxicity and Short-term Toxicity of CITREM

No evidence of mutagenic activity was reported in a study by NICNAS (2001, as cited by JECFA 2015) in which a mixture of citric and lactic acid esters of mono- and diglycerides of fatty acids was tested in an Ames test (i.e., a reverse mutation assay). *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 were tested at concentrations of 50-1000 mcg/plate. NICNAS also reported findings of an acute oral toxicity study with which a single dose of 2000 mg/kg bw of a mixture of citric and lactic acid esters of mono- and diglycerides of fatty acids was administered via gavage to male and female rats and no adverse effects were reported (as cited in GRN 511).

Effects of CITREM on Fat Absorption

The previously described study by the Huntingdon Research Center of rats on a calorie-restricted diet fed the CITREM compound or a physical mixture of its constituents at 23.1 or 37.5% in the diet, or isocaloric diets with 16.7 or 35.5% lard, also included an assessment of fat digestibility (Huntingdon 1966, as cited by FAO 1967). Fat digestibility in the CITREM-treated animals was 47-54% compared to over 90-96% in lard-fed animals and 94-96% in animals fed a standard diet

with a lower fat content (Wheldon et al., 1966, as cited by JECFA 2015). In their recent review, the JECFA Committee noted that the amounts of CITREM fed to animals was high and consequently likely to be associated with nutritional imbalances (JECFA 2015).

The effects of CITREM on intestinal absorption of lipids in adult rats was also examined in a more recent study reviewed by JECFA (Sadouki & Bouchoucha, 2014). In this study, 12 male rats were given a control diet with 30% lipids (15 g palm oil/100 g dry feed), and 12 male rats were given diets in which 30% of lipids were replaced with CITREM or lecithin (10.5 g palm oil plus 4.5 g as CITREM or lecithin; 6 rats/diet). The animals were fed the diets for 9 days. Body weight from start to end of the trial and total feed intake, total fat intake, and total fatty acid intake during the trial did not differ between the treated and control animals. The dry weight of feces from animals fed the CITREM-containing diet was significantly higher than animals fed the control or lecithin-containing diet and there was a corresponding significantly higher concentration of fecal lipids and decrease in apparent lipid absorption. Serum concentrations of phospholipid, triglycerides and total cholesterol were unchanged at the end of the trial. The JECFA panel concluded that these studies of fat absorption in rats were not useful for the safety evaluation given the high concentration of CITREM administered.

Toxicological Data on Related Esters

As previously noted, in the early safety assessment JECFA evaluated evidence pertaining to the safety of acetic acid esters, lactic acid esters, and tartaric acid esters (FAO 1967; WHO 1974). These organic esters of glycerol are structurally similar to CITREM and therefore provide evidence relevant for the safety of CITREM. The available toxicity studies for acetic acid esters included acute studies, short-term studies, and long-term studies, while for tartaric acid esters the available studies included acute and long-term studies; the studies are tabulated in Appendix C. The assessment conducted in GRN 511 discussed the toxicity data as part of the safety review. JECFA acknowledged that interventions with acetic acid esters resulting in dietary perturbations provided little relevance for assessment of toxicity and based the safety determination on evaluation of the biochemical and metabolic studies.

Emulsifiers and Intestinal Barrier Function

It is hypothesized, based primarily on *in vitro* evidence, that food emulsifiers with surfactant activity may affect intestinal barrier integrity, which could have implications for pathogenesis of allergies and autoimmune diseases. In light of this, the recent reviewed completed by JECFA (2015) considered the effect of CITREM on intestinal barrier function. The available evidence was limited by use of high concentrations of emulsifiers (prior to hydrolysis) applied directly to cells, the use of colon cancer-derived cell lines (Caco2) that do not mimic normal physiological conditions, and the lack of any studies specifically on CITREM. Therefore, it was not possible for the Committee to conclude that the intended use of CITREM *in vivo* would affect the intestinal barrier.

Clinical Evidence of Safety

Clinical studies in which infants received infant formula containing CITREM and clinical studies of infants exposed to the hydrolysis products of CITREM, specifically citric acid, provide additional evidence to evaluate the safety of use of CITREM in infant formula.

Clinical Studies of CITREM Intake by Infants

Several clinical trials have been conducted in infant populations consuming infant formula with added CITREM (Table 7). As reviewed by JECFA in 2015 and in GRN 511, clinical trials provided CITREM at concentrations of 95 to 162 mg/100 mL in formula fed to infants or young children for periods of 1 week to an average of nearly 12 months (de Boissieu and Dupont, 2000; de Boissieu and Dupont, 2002; Giampietro et al., 2001; Harvey et al., 2014; Isolauri et al., 1995; Mabin et al., 1995a; Niggemann et al., 2001; Vandenplas et al., 1993; Verwimp et al., 1995). The study populations included infants or young children with cow's milk protein allergy or atopic dermatitis who were fed amino acid or hydrolyzed formulas, and healthy infants fed a hydrolyzed formula. The clinical trials were not designed to assess safety of the CITREM additive, though no adverse effects or untoward effects on growth, hematological, or biochemical measures were reported.

JECFA additionally noted five case reports of infants consuming a peptide-based formula with CITREM at a concentration of 856 mg/100 mL and reported that all infants were observed to gain in weight, length and head circumference and three of the five infants experienced improvements in gastrointestinal symptoms. In GRN 511, Nestle Nutrition also noted the absence of adverse effects in each of three trials presented in abstract form in which infants were provided infant formula reportedly containing CITREM (Gore et al., 2005; Milla et al., 2004; Vandenplas et al., 2011) and in two published studies in which young children consumed hydrolyzed whey or milk formulas reportedly containing CITREM (Mabin et al., 1995b; Vandenplas et al., 2010). Overall, clinical trials in which infants and young children consumed CITREM in a formula or milk-based product provide no evidence of untoward effects under these conditions of use.

Table 7. Clinical Trials Conducted with Infant Formula Containing CITREM

Reference	Study design, target group, dosing regimen and duration	CITREM a (mg/ 100 mL)	Tolerance parameters, adverse effects, relevant clinical parameters
Vandenplas et al (1993)	Double-blind, randomized, controlled trial WHF (containing CITREM) (test group, n=21 [25 randomized and 4 dropped out]) versus whey-predominant formula (control group, n=20) Duration = Birth to 3 months	95 mg/ 100 mL 142.5-190 mg/kg bw/day	No adverse effects reported; no impact on growth, WHF formula containing CITREM results in an adequate nutritional status; increase in iron-binding capacity, zinc and urea (in blood and urine) but no effect on glycemia, proteins, albumin, pre albumin, creatinine, calcium, phosphorus, iron

Reference	Study design, target group, dosing regimen and duration	CITREM a (mg/ 100 mL)	Tolerance parameters, adverse effects, relevant clinical parameters
Verwimp et al (1995)	Double-blind, randomized, controlled trial WHF administered to infants 2-17 weeks of life with cow's milk protein intolerance in control and test group respectively, WHF containing CITREM (n=46) versus other WHF (n=33) Duration = 2.5 months	95 mg/ 100 mL 142.5-190 mg/kg bw/day	No adverse effects reported; no effect on growth; improvement in allergic symptoms
Mabin et al (1995a)	Double-blind, controlled trial Infants and children with refractory atopic dermatitis (median age 2.8 y) receiving WHF formula containing CITREM (n=21, median age 2.8 y) or a casein hydrolysate formula (n=24, median age 1.8 y) Duration = 6 weeks	95 mg/ 100 mL 142.5-190 mg/kg bw/day	No adverse effects reported
Giampietro et al (2001)	Controlled open trial WHF in 32 children (average age 37 months) with cow's milk allergy Duration = 1 week	95 mg/ 100 mL 142.5-190 mg/kg bw/day	No adverse effects reported; WHF containing CITREM well tolerated and considered safe for intended use One child (3%) was unable to tolerate CITREM-containing WHF (experienced urticaria and rhinitis after given test formula)
Isolauri et al (1995)	Double-blind, randomized, controlled trial 22 infants (mean age 6 months) given extensively hydrolyzed whey formula and 23 infants (mean age 7 months) given an amino acid-based formula (containing CITREM) Duration = 9 months	126 mg/ 100 mL 189-276 mg/kg bw/day	No adverse effects reported, no negative effect on growth; test and control formulas considered to be safe and well tolerated; serum biochemistry remained within normal limits
de Boissieu and Dupont (2000)	Amino acid based formula containing CITREM administered to 22 infants with cow's milk protein allergy (mean age 4.6 months) not tolerating other formula with extensively hydrolyzed proteins Duration = average of 11.8 months (range 3-30 months)	138 mg/ 100 mL 252-276 mg/kg bw/day	No adverse effects reported; formula considered to be safe; no negative effect on growth
Niggemann et al (2001)	Randomized, controlled, multi-center trial Infants with cow's milk allergy and atopic dermatitis (median age 5.7 months, range 1.6-9 months) 73 infants either administered an	138 mg/ 100 mL 252-276 mg/kg bw/day	No adverse effects reported; no negative effect on growth

Reference	Study design, target group, dosing regimen and duration	CITREM a (mg/ 100 mL)	Tolerance parameters, adverse effects, relevant clinical parameters
	amino acid-based formula (n=31, containing CITREM) or a formula with extensively hydrolyzed whey formula (n=42) Duration = 6 months		
de Boissieu and Dupont (2002)	Amino acid based formula containing CITREM administered to 52 infants with cow's milk protein allergy (mean age 5.3 months) not tolerating other formula with extensively hydrolyzed proteins (includes cohort from de Boissieu and Dupont (2000)) Duration = average of 11.4 months (range 3.5-41 months)	138 mg/ 100 mL 252-276 mg/kg bw/day	No adverse effects reported; no negative effect on growth
Harvey et al (2014)	Randomized, controlled, multi-center trial Study 1: Amino acid based formulae containing CITREM administered to a total of 70 healthy term infants (birth to 15 days) with or without added synbiotics Duration = 16 weeks	136 mg/ 100 mL 204-272 mg/kg bw/day	No adverse effect linked to product; no negative effect on growth; no effect on tolerance

[a] Information as reported in JECFA 2015; GRN 511. As noted in JECFA 2015 and GRN 511, range of intake on a bodyweight basis was based on a typical formula intake of approximately 150 mL/kg bw per day (FAO/WHO/UNU, 2004) and high intake level of approximately 200 mL/kg bw per day (Fomon, 1993)
WHF – whey hydrolysate formula

Citric Acid

Citric acid has a well-established role as an intermediate metabolite in the tricarboxylic acid cycle (TCA). Citric acid therefore is a normal metabolite in the body and has been considered to present no safety concerns. JECFA established an ADI of "not specified" for citrate (JECFA, 1974), and several citric acid salts are recognized as GRAS, including GMP use in infant formula as well as foods for salts including calcium citrate (21 CFR §184.1195), ferric ammonium citrate (21 CFR §184.1296), ferric citrate (21 CFR §184.1298), ferrous citrate (21 CFR §184.1307c), and manganese citrate (21 CFR §184.1449).

Based on an analysis of 16 infant formulas from the U.S. and Germany, the mean citrate concentration in formula was reported to be 3.34 mmol/L, or approximately 64 mg citric acid per 100 mL formula (Hoppe et al., 1998). In the same study, established lactation human milk was found to contain on average 2.66 mmol/L, or approximately 51 mg citric acid per 100 mL milk (Hoppe et al., 1998). Infants fed breast milk or infant formula are therefore routinely exposed to citrate.

Several clinical studies have examined effects of higher concentrations of citrate consumed by populations of infants and young children. In a randomized controlled study of infants and

young children with acute diarrhea, 54 participants (average age 13.5 months) were fed a hypotonic oral rehydration solution providing approximately 98 mg citrate/kg bw per 24 hours, and 53 participants (average age 16.9 months) were fed a hypotonic solution without citrate. No adverse effects were associated with use of the formula and sodium concentrations in blood and urine and potassium concentrations in blood were comparable between the groups (Rautanen et al., 1994).

In a study designed to examine the effects of alkaline sodium and potassium citrate salts in infant formula on metabolic acidosis in low birthweight, term and preterm infants, 13 infants were fed a demineralized standard formula with added sodium and potassium citrate salts delivering approximately 500 mg citrate/kg bw/day for a period of 3 weeks while 13 infants were fed a standard formula (Berger et al., 1978). The formula with added citrate had no observed effect on growth, adverse effects or tolerance (e.g., vomiting, altered stool frequency) and there were no differences between groups in plasma biochemistry parameters including urea, albumin, calcium, phosphate, and cholesterol. Mild metabolic alkalosis was observed in some infants. Plasma sodium levels in infants fed formula with added citrate varied across the study and transferrin levels on days 11 and 21 were significantly lower than in the control group but still within the normal range.

Another study examined the effects of adding free citric acid by gavage to the diets of infants aged 4-12 months with mild clinical rickets (Smith et al., 1940). Infants also consumed infant formula and weaning feeds which contained citrate. During the periods of citric acid administration, the mean total citrate intakes were 411-707 mg/kg bw per 24 hour period. The investigators noted that four of the eight infants experienced diarrhea during the periods of free citric acid administration, though no other effects were noted. As reviewed by the JECFA Committee, the diarrhea observed in this study may have been a result of the bolus dose administration of citric acid as several studies demonstrate the use of citric acid based oral rehydration solutions (2.94 g trisodium citrate per L or 3.24 g tripotassium citrate per L) to treat diarrhea in infants and adults. Additionally, intake of sodium or potassium citrate (108-430 mg/kg bw/day) by infants and children has been reported in the treatment of urinary infections, hypocitraturia, and kidney studies. Potassium citrate treatment is recognized as a potential irritant of the gut which may result in diarrhea.

In summary, citrates are normal metabolites in the body and found in human milk as well as infant formulas as a component of some salts. Citrates are also present in weaning foods. The available limited evidence indicates that adverse effects of diarrhea are possible with citric acid intake in excess of 400 mg/kg bw/day, though in one study no adverse gastrointestinal effects were observed with intake of approximately 500 mg/kg bw/day citrate salts. The observed occurrence of diarrhea in some studies may in part be an artifact of the bolus exposures that are not representative of formula intake by infants.

Fatty Acids and Glycerol

Following hydrolysis of CITREM, hydrolysis products including glycerol, free fatty acids, and citric acid or related organic acids will be present in the gastrointestinal tract. Glycerol and free fatty acids can be expected to follow the same process of absorption into intestinal cells and

metabolic pathways as they would after the hydrolysis of naturally occurring triglycerides in food. On an energy basis, fat constitutes approximately 50% of the infant diet. Fat is provided in the form of glycerides in human milk or infant formula in a range of chain lengths (Delplanque et al., 2015). The CITREM that is the subject of this review is made with edible palm oil, which consists primarily of palmitic acid and stearic acid. Palmitic, oleic, and linoleic are among the predominant fatty acids in many infant formulas, with typically lower concentrations of a variety of other fatty acids including stearic acid. CITREM is therefore another source of fatty acids typically present in the infant diet.

Summary of Previous Safety Assessments for Use of CITREM in Infant Formula

Use of 233 mg CITREM per 100 mL in exempt amino acid-based and extensively hydrolyzed infant formulas was concluded to be safe and GRAS as detailed in GRN 511. This conclusion was based on a consideration of biochemical characteristics and toxicity studies of CITREM and similar organic esters. As summarized in GRN 511, the available information provides evidence that CITREM is rapidly, though not necessarily completely, hydrolyzed into common dietary components *in vivo* and overall handled in a manner similar to that of triglycerides. Intake of the proposed use of CITREM, corresponding to 482 mg/kg bw/day at the 90th percentile of intake for a young infant, was concluded to be safe. The information on which this conclusion was based was publicly available. Hogan Lovells US LLP independently evaluated the publicly available evidence and concurred with the conclusions reached in GRN 511. More recently, JECFA evaluated the safety of use of higher levels of CITREM in infant formula (up to 900 mg per 100 mL) and concluded them to be safe. The recent review by JECFA supports the safe use of 233 mg CITREM per 100 mL.

Additional Relevant Safety Data

Safety Data since GRN 511 and the 2015 JECFA Review

In the current safety assessment, PubMed searches were conducted to identify relevant papers in the scientific literature since January 1, 2014. Search terms included ("citric acid" OR citrate) AND infant, CITREM, and (citric acid esters) with no limits other than English language. The searches were most recently updated though January 20, 2019 (search strings are presented in Appendix D). No new information relevant for the safety assessment was identified in the searches, thus there is no evidence to call into the question the previous conclusions of safety for the intended uses.

Biochemical Handling of CITREM by Infants Consuming Calorically Dense Infant Formula

The intended use of CITREM is as an emulsifier in energy dense, exempt infant formula for term infants with special nutritional requirements and/or who require a fluid restriction. The nutrient dense formula is a high-energy formulation intended for use in term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism.

Term infants consuming the energy dense formula with CITREM would reasonably digest and metabolize triglycerides as do other term infants consuming breast milk or standard infant formula. The biochemical aspects of CITREM considered in previous safety assessments for use of CITREM in infant formula are therefore applicable, and it follows that infants consuming the energy dense exempt infant formula would handle CITREM as would other term infants.

GRAS Criteria

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

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

In the preamble to the final rule for GRAS notifications, FDA stated that a GRAS conclusion, based on scientific procedures may be supported by scientific data (such as human, animal, analytical or other scientific studies), information, methods and principles, published or unpublished, appropriate to establish the safety of a substance under the conditions of intended use (FDA, 2016). The safety standard requires that there be a reasonable certainty of no harm under the conditions of intended use of the substance. To be eligible for a GRAS conclusion based on scientific procedures, there must be evidence of a consensus among qualified experts that the proposed use is safe and the pivotal data and information supporting the safety of the ingredient's intended use must be publicly available.

Safety Assessment

The safety of the intended use of CITREM at a maximum level of 233 mg CITREM per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction can be assessed by consideration of the established safety of CITREM in infant

formula based on the biochemical characteristics of CITREM and evidence regarding toxicity and the estimated intake of CITREM and citric acid from the proposed use.

The available evidence demonstrates that CITREM is rapidly and substantially hydrolyzed in the gastrointestinal tract to common dietary components of the infant diet, namely fatty acids, glycerol and citric acid. It is reasonable to conclude that any remaining partially hydrolyzed products do not present a safety concern. Assuming the proposed maximum use of CITREM of 233 mg per 100 mL, the estimated daily intake of CITREM is 408 mg/kg bw/day based on a conservatively high estimated formula intake of 175 kcal/kg bw. This level of CITREM intake is below levels previously concluded to be GRAS (i.e., 482 mg/kg bw/day) as detailed in GRN 511, and also below levels of CITREM intake that JECFA concluded to present no toxicological concerns when used in infant formula (i.e., 599 mg/kg bw/day for very young male infants consuming 270 mg CITREM per 100 mL infant formula).

The total estimated intake of citric acid from formula, including citric acid from the proposed maximum use of CITREM and citric acid from other ingredients typical in infant formula and the maximum permitted concentration of citric acid in CITREM (i.e., 50%) is estimated at 316 mg citric acid per kg bw/day. This level of citric acid intake is below the range associated with diarrhea and therefore unlikely to present concerns for an adverse effect. Specifications for levels of impurities potentially present in CITREM, namely environmental contaminants (PAHs, dioxins, sum of dioxins and dioxin-like PCBs, non dioxin-like PCBs), as well as microbiological contaminants, are set at levels to ensure they do not present safety concerns for food ingredients.

The intended use of 233 mg CITREM per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction therefore can be concluded to be safe.

Conclusion Regarding Safety and General Recognition of Safety

CITREM is a mixture of citric acid esters and fatty acid esters. The citric acid esters are similar in structure to triglycerides, with the exception of at least one citric acid moiety substituted for a fatty acid moiety while the fatty acid esters in CITREM bear structural similarity to naturally occurring triglycerides found in food. CITREM therefore is a mixture of various common glycerides.

The safety of the use of CITREM, including use in infant formula, has been comprehensively evaluated by authoritative bodies including the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Union's Scientific Committee on Food (SCF), and Health Canada. In the U.S., the use of 233 mg CITREM per 100 mL in exempt amino acid-based and extensively hydrolyzed infant formulas was concluded to be safe and GRAS. The U.S. Food and Drug Administration was notified of this determination and responded with a letter of no concern (FDA 2014).

The safety of the proposed use of up to 233 mg CITREM per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction was evaluated in this GRAS review. The intended use level of CITREM in this GRAS evaluation is therefore

identical to a recognized safe use of the ingredient and expands only the types of infant formula to which the ingredient would be added. The estimated intake of CITREM is below the level previously concluded to be safe, and the level of citric acid intake is below levels associated with the potential for diarrhea.

The CITREM proposed for use is manufactured from food-grade materials under GMP and analytical data demonstrate that the product meets established specifications. The safety of the use of CITREM in infant formula has been established through consideration of the physiological nature of the substance and its metabolites in the context of infant digestion, and potential exposure to citric acid from CITREM. The toxicity of CITREM is intrinsically low. It is therefore reasonable to conclude that the proposed use of CITREM as an emulsifier at a maximum level of 233 mg per 100 mL in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is safe within the meaning of 21 CFR §170.3(i), i.e., meets the standard of reasonable certainty of no harm.

General recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of food ingredients that there is a reasonable certainty that a substance is not harmful under the conditions of its intended use in foods. The regulatory and scientific reviews needed to establish the safety of the intended use of CITREM are published in the scientific literature and, therefore, are generally available to the community of qualified food ingredient safety experts. There is broad-based and widely disseminated knowledge concerning CITREM. The publicly available data and information supporting the safety of the intended use of CITREM as specified in this document are not only generally available, but are also generally accepted among qualified food safety experts. The proposed use of CITREM therefore can be concluded to be safe and generally recognized as safe (GRAS) through scientific procedures.

Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the proposed use of CITREM, meeting appropriate specifications specified herein and used according to Good Manufacturing Practice (GMP), is GRAS.

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

References

Amara S, Patin A, Giuffrida F, Wooster TJ, Thakkar SK, Bénarouche A, Poncin I, Robert S, Point V, Molinari S, Gaussier H, Diomande S,Destaillats F, Cruz-Hernandez C, Carrière F. In vitro digestion of citric acid esters of mono- and diglycerides (CITREM) and CITREM-containing infant formula/emulsions. Food Funct. 2014 Jul 25;5(7):1409-21.

Ambrose AM, Robb DJ. Studies on comparative absorption and digestibility of acetoglycerides. J Nutr. 1956b Jan 10;58(1):113-24.

Ambrose AM, Robbins DJ, Cox Jr AJ. Studies on the long-term feeding of acetoglycerides to rats. Food Res. 1958a 23:536-541.

Ambrose AM, Robbins DJ, Deeds F. Effect of acetostearin on reproduction in albino rats. Food Res. 1958b. 23:550-554.

Ambrose AM, Robbins DJ. Studies on the toxicity of acetoglycerides. J Am Pharm Assoc. 1956a. 45:282-284

Berger HM, Scott PH, Kenward C, Scott P, Wharton BA. Milk pH, acid base status, and growth in babies. Arch Dis Child. 1978 Dec;53(12):926-30.

Clarke SE, Evans S, Macdonald A, Davies P, Booth IW. Randomized comparison of a nutrient-dense formula with an energy-supplemented formula for infants with faltering growth. J Hum Nutr Diet. 2007 Aug; 20(4): 329-39.

CODEX Alimentarius. GSFA Online. Updated up to the 40th Session of the Codex Alimentarius Commission, 2017. Food Additive Details. Citric and fatty acid esters of glycerol (472c); pp 125-126. http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/gsfa/en/. Accessed January 17, 2019.

CODEX Alimentarius. Standard for infant formula and formulas for special medical purposes intended for infants. CODEX STAN 72-1981. Formerly CAC/RS 72-1972. Adopted as a worldwide Standard in 1981. Amendment: 1983, 1985, 1987, 2011, 2015 and 2016. Revision: 2007.

Coleman RD, LA Gayle, RB Ah-Slater. A nutritional evaluation of acetostearine intake. J Am Oil Chem Soc. 1963 40:737-742.

Cui Y, Li L, Hu C, Shi H, Li J, Gupta RK, Liang H, Chen X, Gong S. Effects and Tolerance of Protein and Energy-Enriched Formula in Infants Following Congenital Heart Surgery: A Randomized Controlled Trial. JPEN J Parenter Enteral Nutr. 2018 Jan;42(1):196-204.

de Betue CT, van Waardenburg DA, Deutz NE, van Eijk HM, van Goudoever JB, Luiking YC, Zimmermann LJ, Joosten KF. Increased protein-energy intake promotes anabolism in critically ill infants with viral bronchiolitis: a double-blind randomised controlled trial. Arch Dis Child. 2011 Sep;96(9):817-22.

de Boissieu D, Dupont C. Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. J Pediatr. 2002 Aug;141(2):271-3.

de Boissieu D, Dupont C. Time course of allergy to extensively hydrolyzed cow's milk proteins in infants. J Pediatr. 2000 Jan;136(1):119-20.

Delplanque B, Gibson R, Koletzko B, Lapillonne A, Strandvik B. Lipid Quality in Infant Nutrition: Current Knowledge and Future Opportunities. J Pediatr Gastroenterol Nutr. 2015 Jul;61(1):8-17.

European Union (EU). Commission Regulation (EU) No 1129/2011 (2011).

Eveleens RD, Dungen DK, Verbruggen SCAT, Hulst JM, Joosten KFM. Weight improvement with the use of protein and energy enriched nutritional formula in infants with a prolonged PICU stay. J Hum Nutr Diet. 2019 Feb;32(1):3-10.

Food and Agricultural Organization of the U.N. (FAO) Nutrition Meetings. 1967. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilisers, flour-treatment agents, acids and bases. Report Series No. 40A,B,C, WHO/Food Add./67.29. Geneva: FAO/WHO.

Food Standards Australia New Zealand (FSANZ). Permitted uses of food additives by food type. http://www.foodstandards.gov.au/code/Documents/standard_1_3_1_additives_vol_2_v1321.pdf

Fye DJ, Katz HC. 1953. Unpublished report submitted to WHO; cited in FAO 1967 and WHO 1974.

Giampietro PG, Kjellman NIM, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. Pediatr Allergy Immunol. 2001 Apr;12(2):83-6.

Gongwer LE. 1959. Unpublished report submitted to WHO; cited in FAO 1967 and WHO 1974.

Gore C, G Kerry, KH Johnson, D Grathwohl, J Morris, G Tannock, P Arkwright, A Custovic, A Woodcock. 2005. Probiotics in Atopic Dermatitis in Infancy (PADI) Study: Lactobacillus paracasei and Bifidobacterium lactis do not improve the short-term clinical outcome of atopic dermatitis. Allergy Clin Immunol Int S1:54. (Abstract)

Harvey BM, Langford JE, Harthoorn LF, Gillman SA, Green TD, Schwartz RH, Burks AW. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. Pediatr Res. 2014 Feb;75(2):343-51

Health Canada. Information Document on Health Canada's Proposal to Amend the Food and Drug Regulations to Permit the use of Citric Acid Esters of Mono- and Diglycerides (1) as a Food Additive in Infant Formulae For Special Medical Purposes; and (2) in those Foods that are Currently Permitted to Contain Monoglyceride Citrate. Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch. November 2010.

Hoppe B, Roth B, Bauerfeld C, Langman CB. Oxalate, citrate, and sulfate concentration in human milk compared with formula preparations: influence on urinary anion excretion. J Pediatr Gastroenterol Nutr. 1998 Oct;27(4):383-6.

Huntingdon Research Centre. 1966. Unpublished report submitted to JECFA by Emulsion AB; cited in FAO 1967 and WHO 1974.

INGROTO: Effects of a nutrient dense infant formula on the growth and tolerance of infants compared to current practice in Spain (data on file). 2012. (internal report).

Institute of Medicine (IOM). Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acid. 2002. National Academies Press: Washington, DC.

Isolauri E, Sutas Y, Makinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. J Pediatr. 1995 Oct;127(4):550-7.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). Toxicological evaluation of certain food additives with a review of general principles and specifications (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2015. Seventy-Ninth Report. Evaluation of Certain Food Additives. WHO Food Additives Series 70. Geneva: World Health Organization.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). Joint FAO/WHO Expert Committee on Food Additives. Compendium of food additive specifications, FAO JECFA Mono graph 19. 82nd Meeting 2016. FAO/WHO. Rome.

Kaunitz H. 1958. Unpublished report submitted to WHO; cited in FAO 1967 and WHO 1974.

Keefe DM. Agency Response Letter GRAS Notice No. GRN 000511. CFSAN/Office of Food Additive Safety. November 10, 2014.

https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=511&sort=GRN_No&order=DESC&startrow=1&type=basic&search=511.

Kieckebusch W, Czok G, Griem W, Lang K. [On the biologic effect of corn oil after heating under kitchen technical conditions]. Z Ernahrungswiss. 1968 May;9(1):49-66. German; cited in FAO 1967 and WHO 1974.

LAMIRSA. GRAS Notification for Citric acid esters of mono- and diglycerides. Filed May 1, 2007 as GRN No. 222.
https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=222&sort=GRN_No&order=DESC&startrow=1&type=basic&search=222.

Mabin DC, Sykes AE, David TJ. Controlled trial of a few foods diet in severe atopic dermatitis. Arch Dis Child. 1995b Sep;73(3):202-7.

Mabin DC, Sykes AE, David TJ. Nutritional content of few foods diet in atopic dermatitis. Arch Dis Child. 1995a Sep;73(3):208-10.

Mattson FH, Alexander JC, Baur FJ, Reller HH. Short-term feeding studies on acetin fats. J Nutr. 1956 Jun 10;59(2):277-85.

McKennis H Jr, Turnbull LB, Haag HB, Larson PS. Metabolism of lactic acid and glycerol in C14-glyceryl lactopalmitate. Proc Soc Exp Biol Med. 1958Mar;97(3):498-501.

Milla PJ, Schappi M, Flack S, Hascke F, Steenhout P, Carpino M, Lawson M. A new semi-elemental diet for small intestinal inflammatory disease. J Pediatr Gastroenterol Nutr 2004 39:S278. (Abstract).

Minister of Justice. Food and Drug Regulations, C.R.C., c. 870. Current to December 12, 2018, Last amended on November 23, 2018. Accessed January 17, 2019 at http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html.

Mosinger M. 1965. Unpublished report submitted to JECFA, cited in FAO 1967, WHO 1974, and SCF 1978.

Nestle Nutrition, U.S. GRAS Determination for the Addition of Citric Acid Esters of Mono- and Diglycerides to Exempt Infant Formula As Antioxidants, Emulsifiers, Stabilizers and Thickeners. Filed April 23, 2014 as GRN No. 511.
https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=511&sort=GRN_No&order=DESC&startrow=1&type=basic&search=511.

Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. Pediatr Allergy Immunol. 2001 Apr;12(2):78-82.

Rautanen T, Salo E, Verkasalo M, Vesikari T. Randomised double blind trial of hypotonic oral rehydration solutions with and without citrate. Arch Dis Child. 1994 Jan;70(1):44-6.

Rosner L. 1959. Unpublished report submitted to JECFA by the Laboratory of Vitamin Technology; cited in FAO 1967 and WHO 1974.

Sadouki M, Bouchoucha M. Changes of lipid and fatty acid absorption induced by high dose of citric acid ester and lecithin emulsifiers. Int J Food Sci Nutr. 2014 Sep;65(6):728-32.

Scientific Committee on Food (SCF). 1998. Oinion of the Scientific Committee for Food on Certain Additives for Use in Foods for Infants and Young Children in Good Health and in Foods for Special Medical Purposes for Infants and Young Children". Reports of the Scientific Committee for Food (43rd Series). Commission of the European Communities, Luxembourg.

Scientific Committee on Food (SCF). 2002. Opinion of the Scientific Committee on Food on Citric acid esters of mono- and diglyglycerides (E472c): request for additional uses in foods for special medical purposes for infants and young children. SCF/CS/ADD/MsAd/221 Final 17 Sept 2002. Commission of the European Communities, Luxembourg.

Smith AH, Barnes DJ, Meyer CE, Kaucher M. The metabolism of citric acid by infants. J Nutr. 1940. 20:255‑62.

Tarantino LM. Agency Response Letter GRAS Notice No. GRN 000222. CFSAN/Office of Food Additive Safety. December 20, 2007. https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=222&sort=GRN_No&order=DESC&startrow=1&type=basic&search=222.

Treon JF, Myron Brin M, Domingues FJ, Smullin CF, Lowry JR, Helmick M. Food Additive Safety, The Metabolism of Glyceryl Lactate-C14-Palmitate by Rats. Journal of Agricultural and Food Chemistry. 1962 10 (2), 111-120.

van Waardenburg DA, de Betue CT, Goudoever JB, Zimmermann LJ, Joosten KF. Critically ill infants benefit from early administration of protein and energy-enriched formula: a randomized controlled trial. Clin Nutr. 2009 Jun;28(3):249-55.

Vandenplas Y, Grathwohl D, Steenhout P, Christens J, Halut C, Mulier S, Marien P, Veereman G, Kamoen K, Peeters S, Smets F, Bury F, Verghote M, Bollen P, Beauraind O, Lenoir P, Colinet S, Van Winckel M. Comparison of two extensively hydrolyzed formulas for the treatment of children with cow's milk intolerance. J Pediatr Gastroenterol Nutr. 2011 52 Suppl 1: E160-161.

Vandenplas Y, Hauser B, Blecker U, Suys B, Peeters S, et al. The nutritional value of a whey hydrolysate formula compared with a whey-predominant formula in healthy infants. J Pediatr Gastroenterol Nutr. 1993 Jul;17(1):92-6.

Wheldon GH, Ginn HB, Leahy JS, Mawdesley-Thomas LE (1966). The response of calorie restricted rats to Palsgaard 3301. Huntingdon Research Centre, Huntingdon, England, United Kingdom. 15 April 1966. Unpublished report. Submitted to WHO by the European Food Emulsifiers Manufacturers Association, Brussels, Belgium, as an Annex to EFEMA, 2014; cited in JECFA 2015.

World Health Organization (WHO). 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. WHO Food Additives Series No. 5. Geneva: FAO/WHO.

Appendices

Appendix A. Analytical Data from Representative Batches of CITREM

[redacted]

Statement

Supplier : [redacted]

Product type : Emulsifier

Country of Production : [redacted]

Please be informed that [redacted] CITREM [redacted] is an approved food additive and is in compliance with the specifications laid down by EU under E472c and JECFA under INS 472c and the Food Chemical Codex for "Citric and Fatty Acid Esters of Glycerol":

	EU	JECFA	FCC	[redacted] specification	Analysis results for 093224 batch 4012692136	Analysis results for 093224 batch 4012465697	Analysis results for 093224 batch 4013014634
Regulatory Requirements:							
Acids other than citric and fatty acids (%)	<1			<1	Pass	Pass	Pass
Total citric acid (%)	13-50	13-50	13-50	13-50	15	15	15
Total glycerol (%)	8-33	8-33	8-33	8-33	25	23	24
Free glycerol (%)	Max 2	Max 4	Max 4	Max 2	1,1	0,8	0,9
Total fatty acids (as oleic acid) (%)		37-81	37-81	37-81	*	*	*
Sulphated ash (800 +/- 25°C) (%)	Max 10	Max 10	Max 10	Max 10	2,3	2,2	2,3
Lead (ppm)	Max 2	Max 2	Max 2	Max 2	0,4	0,8	0,4
Acid Value (mgKOH/g)	Max 130			10-25	14	14	9
Additional Sales Specifications:							
Arsenic (ppm)				Max 1,5	1,0	1,0	0,5
Mercury (ppm				Max 1	0,1	0,1	0,1
Cadmium (ppm)				Max 1	0,1	0,2	0,1
Saponification Value (mgKOH/g)				220-250	240	240	240
Iodine Value				Max 3	*	*	*
pH in 5% aqueous dispersion				5-6	*	*	*
Dropping point (°C)				Approx 64	*	*	*

[redacted]

[redacted]

Microbiological specifications					Analysis results for 093224 batch 4012958890	Analysis results for 093224 batch 4012833714	Analysis results for 093224 batch 4012601927
Total Plate Count (/g)				Max 5000	100	100	100
Yeast and mould (/g)				Max 100	10	10	10
Enterobacteria (abs. in 1 g)				Pass	Pass	Pass	Pass
Salmonella (abs. in 1 g)				Pass	Pass	Pass	Pass

*controlled via raw materials to be within specifications.

Production process information:

[redacted] CITREM [redacted] is produced by reaction of mono- and diglycerides of edible fatty acids (produced from glycerol and fully hydrogenated palm oil) with citric acid.
The product is partially neutralized with sodium-acetate.
The product is spray-cooled into a coarse powder and packed in 20 kg paper bags.
Each bag goes through metal-detector (CCP)
Please see attached flow-diagram (follow green line) and attached HACCP-plan for the Spray-area (finished product area)

Raw materials:

[redacted] CITREM [redacted] is produced from following food grade raw materials:
Fully refined, hydrogenated, edible palm oil (food grade)
Glycerol (currently from rapeseed) - comply with food additive E422
Citric acid (produced by microbial fermentation) - comply with food additive E330
Sodium Acetate - comply with food additive E262 (i)

Brabrand, 7 February 2019

[redacted]

Appendix B. Controls for Potential Contaminants

[redacted]

[redacted]

Statement on PAHs, Dioxin and Dioxin-like PCBs

Supplier : [redacted]

Product type :

Country of Production :

Commission Regulation (EC) 1881/2006 of 19 December 2006 as amended, setting maximum levels for PAH's, dioxins, dioxin-like PCBs and non dioxin-like PCBs in foodstuffs

We can inform you that we have guarantees from our fat and oil suppliers that they comply with EU legislation for fats and oils. Furthermore, they produce according to Fediol guidance.

[redacted]

PAH

Oils and fats: BaP max. 2 ppb
Sum of PAH4 (benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene) max. 10 ppb

Sum of dioxins

Vegetable oils and fat: max. 0.75 pg WHO-PCDD/F-TEQ/g fat

Sum of dioxins and dioxin-like PCBs

Vegetable oils and fat: max. 1.25 pg WHO-PCDD/F-PCB-TEQ/g fat

Sum of non dioxin-like PCBs

Vegetable oils and fat: max. 40 ng ICES-6/g fat

Brabrand, 4 January 2017

[redacted]

[redacted]

[redacted]

[redacted]

Pesticides Residuals

Supplier : [redacted]

Product type :

Country of Production :

The European Union and other international regulatory bodies have established maximum residue limits for agricultural chemicals in food products. It is the responsibility of the user of agricultural chemicals to incorporate only approved agricultural chemicals into their crop treatment programs, and to do so according to requirements and at levels specified by applicable regulations and manufacturer's instructions. Administration of such a program should result in conformance of agricultural chemical residue levels to established regulatory limits.

We have guarantees from our suppliers of fats, oils and fatty acids that they comply with the EU requirements laid down by Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin.

An accredited external third party laboratory monitors a possible presence of banned or regulated agricultural chemicals in our raw materials sourced from palm, rapeseed, sunflower, castor, soy or coconut. None of the pesticides screened for was found at levels above the stated quantification limits of the multi residue analysis package and individual compound analyses.

Classes of pesticides screened for:

- Organochlorine pesticides incl. pyrethroids
- Organophosphorous pesticides
- Organonitrogen pesticides
- Non-dioxinlike polychlorinated biphenyls

Brabrand, 8 February 2017

[redacted]

[redacted]

Monitory report 2016

[redacted]

Screened Pesticides Residuals

Organochlorine Pesticides incl Pyrethroids	LOQ (mg/kg)
2.3.4.6-Tetrachloranisol	0.005
Aclonifen	0.01
Acrinathrin	0.05
Aldrin	0.005
Benfluralin	0.005
Benzoylprop-ethyl	0.01
Bifenox	0.02
Bifenthrin	0.05
Binacapryl	0.02
Bromocyclen	0.01
Bromoxynil-octanoate	0.01
Butralin	0.02
Chlordane, cis-	0.005
Chlordane, oxy-	0.005
Chlordane, trans-	0.005
Chlorfenapyr	0.01
Chlorfenprop-methyl	0.02
Chlorfenson	0.01
Chloroneb	0.02
Chlorothalonil	0.01
Chlorthal-dimethyl	0.005
Cyfluthrin	0.05
Cyhalothrin, lambda	0.05
Cypermethrin	0.05
Cyphenothrin	0.05
DDD, o,p-	0.005
DDD, p,p'-	0.005
DDE, o,p-	0.005
DDE, p,p'-	0.005
DDT, o,p'-	0.005
DDT, p,p'-	0.005
Deltamethrin	0.05
Dibromobenzophenone, p,p-	0.02
Dichlobenil	0.01
Dichlorobenzophenone, o,p-	0.02
Dichlorobenzophenone, p,p-	0.02
Dicloran	0.005
Dicofol, o,p-	0.02
Dicofol, p,p-	0.02
Dieldrin	0.005
Dienochlor	0.01
Dinitramine	0.01
Dinobuton	0.02
Endosulfan sulphate	0.01
Endosulfan, alpha	0.005
Endosulfan, beta	0.005
Endrin	0.005
Endrine ketone	0.01
Ethalfluralin	0.01
Etridiazole	0.01
Fenfluthrin	0.05
Fenpropathrin	0.05
Fenson	0.01
Fenvalerate (RR-/SS-Isomers)	0.05
Fenvalerate (RS-/SR-Isomers)	0.05
Flubenzimine	0.01
Fluchloralin	0.01
Flucythrinate	0.05
Flumetralin	0.01
Flurodifen	0.01
Fluromide	0.02
Genite	0.01
HCH, alpha-	0.005
HCH, beta-	0.005
HCH, delta-	0.005
HCH, epsilon-	0.005
Heptachlor	0.005
Heptachlor epoxide, cis-	0.005
Heptachlor epoxide, trans-	0.005
Hexachlorobenzene (HCB)	0.005
Ioxynil-Octanoate	0.01
Isobenzan	0.005
Isodrin	0.005
Isopropalin	0.01
Lindane (gamma-HCH)	0.005
Methoxychlor	0.01
Mirex	0.005
Nitrapyren	0.01
Nitrofen	0.01
Nonachlor, trans-	0.005
Octachlorstyrene	0.005
Oxyfluorfen	0.01
Pendimethalin	0.01
Pentachloranisole	0.005
Pentachloraniline	0.005
Pentachlorobenzene	0.01
Pentachlorothioanisole	0.005
Permethrin	0.05
Plifenate	0.02
Polychloroterpene	0.5
Profluralin	0.005
Quintozene	0.005
S 421	0.01
Tau-Fluvalinate	0.05
Tecnazene	0.005
Tefluthrin	0.05
Tetradifon	0.01
Tetrasul	0.01
Tralomethrin	0.05
Transfluthrin	0.05
Triallate	0.02
Trichloronat	0.01
Trifluralin	0.005
Organophosphorus Pesticides	**LOQ (mg/kg)**
Acephate	0.02
Azinphos-ethyl	0.05
Azinphos-methyl	0.05
Bromofenvinphos	0.02
Bromophos-ethyl	0.02
Bromophos-methyl	0.02
Butamifos	0.02
Cadusaphos	0.02
Carbophenothion	0.02
Carbophenothion-methyl	0.02
Chlorfenvinphos	0.02
Chlormephos	0.02
Chlorpyrifos (-ethyl)	0.02
Chlorpyrifos-methyl	0.02
Chlorthion	0.02
Organophosphorus Pesticides (continued)	**LOQ (mg/kg)**
Chlorthiophos	0.02
Coumaphos	0.1
Crotoxyphos	0.02
Crufomate	0.02
Cyanofenphos	0.05
Cyanophos	0.02
Demeton-S-methyl	0.05

Demeton-S-methyl-sulfone	0.1
Dialifos	0.02
Diazinon	0.02
Dicapthon	0.02
Dichlofenthion	0.02
Dichlorvos	0.02
Dicrotophos	0.02
Dimefox	0.02
Dimethoat	0.02
Dimethylvinphos	0.02
Dioxabenzofos	0.02
Dioxathion	0.05
Disulfoton	0.05
Disulfoton-sulfon	0.05
Ditalimfos	0.02
Edifenphos	0.05
Ethion	0.02
Ethoprophos	0.02
Etrimfos	0.02
Fenamiphos	0.02
Fenamiphos-sulfone	0.05
Fenamiphos-sulfoxide	0.05
Fenchlorphos	0.02
Fenchlorphos oxon	0.02
Fenitrothion	0.02
Fensulfothion	0.02
Fensulfothion-oxon-sulfone	0.05
Fensulfothion-oxon-sulfoxide	0.05
Fenthion	0.02
Fenthion-oxon-sulfone	0.05
Fenthion-oxon-sulfoxide	0.05
Fenthion-sulfone	0.05
Fenthion-sulfoxide	0.05
Fonofos	0.02
Formothion	0.02
Fosthiazate	0.05
Fosthietan	0.02
Heptenophos	0.02
Iodofenphos	0.05
Iprobenfos	0.02
Isazophos	0.02
Isocarbofos	0.02
Isofenphos	0.02
Isofenphos-methyl	0.02
Isoxathion	0.05
Leptophos	0.05
Malaoxon	0.02
Malathion	0.02
Mecarbam	0.02

Mephosfolan	0.02
Merphos	0.02
Methacriphos	0.02
Methamidophos	0.02
Methidathion	0.02
Mevinphos	0.02
Monocrotophos	0.02
Morphothion	0.05
Omethoate	0.02
Oxydemeton-methyl	0.1
Paraoxon-ethyl	0.02
Paraoxon-methyl	0.02
Parathion	0.02
Parathion-methyl	0.02
Phenkapton	0.05
Phenthoate	0.02
Phorate	0.02
Phorate-sulfone	0.05
Phorate-sulfoxide	0.05
Phosalone	0.05
Phosmet	0.05
Phosphamidon	0.02
Pirimiphos-ethyl	0.02
Pirimiphos-methyl	0.02
Profenofos	0.02
Propaphos	0.02
Propetamphos	0.02
Prothiofos	0.02
Prothoate	0.02
Pyraclofos	0.05
Pyrazophos	0.05
Pyridaphenthion	0.02
Quinalphos	0.02
Quintiofos	0.02
Sulfotep	0.02
Sulprofos	0.05
TEPP	0.02
Terbufos	0.02
Terbufos-sulfone	0.05
Tetrachlorvinphos	0.02
Thiometon	0.02
Tolclofos-methyl	0.02
Triamiphos	0.05
Triazophos	0.02
Trichlorfon	0.1
Vamidothion	0.05

Organonitrogen Pesticides	**LOQ (mg/kg)**
2-Phenylphenol	0.03
Alachlor	0.03
Ametryn	0.03
Aminocarb	0.03
Atrazine	0.03
Benalaxyl	0.03
Bendiocarb	0.03
Biphenyl	0.03
Bitertanol	0.03
Bromacil	0.03
Bromopropylate	0.03
Bupirimate	0.03
Buprofezin	0.03
Carbaryl	0.03
Carbofuran	0.03
Chloridazone	0.03
Chlorobenzilate/Chloropropylate	0.03
Chlorpropham	0.03
Cyanazine	0.03
Cyproconazole	0.03
Desmetryn	0.03
Dichlobenil	0.03
Dichlofluanid	0.03
Diflubenzuron	0.03
Dimethylaminosulphotoluidide	0.03
Dimethylphenylsulfamide	0.03
Dioxacarb	0.03
Diphenylamine	0.03
Diuron/Linuron/Neburon	0.03
Etofenprox	0.03
Organonitrogen Pesticides (continued)	**LOQ (mg/kg)**
Fenarimol	0.03
Fenazaquin	0.03
Fenoxycarb	0.03
Fenpropimorph	0.03
Fluazifop-P-butyl	0.03
Flusilazole	0.03
Furathiocarb	0.03
Hexaconazole	0.03
Hexazinone	0.03
Iprodione	0.03
Lenacil	0.03
Metalaxyl	0.03
Methabenzthiazuron	0.03
Methiocarb	0.03
Metolachlor	0.03

Metribuzin	0.03
Myclobutanil	0.03
Oxadiazon	0.03
Oxadixyl	0.03
Penconazole	0.03
Pirimicarb	0.03
Pendimethalin	0.03
Piperonyl butoxide	0.03
Pirimicarb, desmethyl-	0.03
Procymidone	0.03
Promecarb	0.03
Prometryn	0.03
Propachlor	0.03
Propargite	0.03
Propazine	0.03
Propham	0.03
Propiconazole	0.03
Propoxur	0.03
Propyzamide	0.03
Pyrimethanil	0.03
Sebuthylazine	0.03
Simazine	0.03
Tebuconazole	0.03
Teflubenzuron	0.03
Terbuthylazine	0.03
Terbutryn	0.03
Tetradifon	0.03
Tetrahydrophthalimide	0.03
Tolylfluanid	0.03
Triadimefon	0.03
Triadimenol	0.03
Triflumizole	0.03
Triflumuron	0.03
Trifluralin	0.03
Trinexapac-ethyl	0.03
Vinclozolin	0.03

Non-dioxinlike Polychlorinated Biphenyls	**LOQ (mg/kg)**
IUPAC-Nr 118	0.02
PCB IUPAC 101	0.02
PCB IUPAC 138	0.02
PCB IUPAC 153	0.02
PCB IUPAC 180	0.02
PCB IUPAC 28	0.02
PCB IUPAC 52	0.02

Appendix C. Toxicological Studies on Esters Structurally Similar to CITREM

Substance	Test	Findings	Reference
Acetic acid esters	Acute toxicity: Single dose of 4000 mg/kg bw of a mixture ofacetostearin and acetoolein in mature rats (10 male, 10 female)	No toxic symptoms observed.	Ambrose & Robbins 1956a
Acetic acid esters	Acute toxicity: Daily i.v. injections of 80-100 mg acetosterin in rabbits for 15 days	No apparent ill effects observed; no pathological changes in viscera; acetostearin cleared from plasma within 15-30 minutes.	Ambrose & Robbins 1956a
Acetic acid esters	Short-term study: Male weanling rats (10/group) received diets containing 25% stearin, olein, diacetostearin, or diactoolein; other groups received diets containing 50% olein or diacetoolein for 8 weeks, or 15% acetoolein for 12 weeks	No effect of diet on body weight gain or food consumption. Feed utilization efficiency was higher in rats fed diaceostearin. Blood and urine were normal.	Mattson et al., 1956
Acetic acid esters	Short-term study: Rats (5 male and 10 female/group) received diets containing 10% acetostearin with or without additional vitamin E for 7 months	Improved reproductive performance in rats fed aceostearin with vitamin E (increased litter number numbers and pups per litter in four successive matings) compared with controls or aceostearin alone.	Ambrose et al., 1958b
Acetic acid esters	Long-term study: Weanling male rats (5/group) were fed diets containing 0, 0.25, 0.5, 1, 2 or 4% acetostearin, and other rats were fed diets containing 0, 0.25, 0.5 or 1.0% acetoolein for 57 weeks.	No effect of diet on body weight gain, food intake or mortality. No effect of diet on relative weights of major organs other than testes; decreased testicular weights at all levels of acetoolein and with the 0.25 and 0.5% levels of acetostearin. No effect of diet on gross microscopic effects other than for testes; testicular hypoplasia and suppression of spermatogenesis of a variable degree observed in all test groups. Observed effects were attributed to vitamin E insufficiency.	Ambrose & Robbins 1956a
Acetic acid esters	Long-term study: Rats (10 male and 10 female/group) were fed diets with at 0, 5, 10 and 20% of one of 3 acetostearins or one of 2 acetooleins. Parental generation animals on 20%	Overall various pathological changes were observed with individual acetoglycerides at varying dietary levels, and fatty tissue changes indicative of foci of foreign body reactions with all acetostearins at 20% level. The changes were attributed to	Ambrose et al., 1958a

Substance	Test	Findings	Reference
	acetoglyceride were sacrificed after 57 weeks, 86 weeks and 101 weeks.	imbalances of dietary vitamin E and essential fatty acids rather than the test articles.	
Lactic acid esters	Acute toxicity: Rats (6 male/group) were given GLP suspended in water via intubation at doses of 8.65 or 5.75 g/kg bw.	All animals survived, and no systemic effects were observed other than effects attributable to mechanical distension. Gross appearance of major organs was normal after 14 days	Gongwer 1959*
Lactic acid esters	Short-term study: Various unspecified experiments with small numbers of rats.	No toxic effects revealed.	Kaunitz 1958*
Lactic acid esters	Long-term study: Various unspecified experiments with small numbers of rats.	No toxic effects revealed.	Fye & Katz 1958*
Tartaric acid esters	Acute toxicity: Mice given oral dose of product containing 16% tartaric acid ester, 44% fat, 20% glucose, 20% sucrose.	LD_{50} study = 20,000 mg/kg bw (3200 mg/kg bw of the ester)	Kieckebusch et al., 1968**
Tartaric acid esters	Long-term study: Wistar rats (15 male and 15 females) fed diets containing 0 or 0.8% ester for 24 months.	No effects observed with food consumption, body weight, external appearance, mortality, or reproduction; no effects observed in histological exams attributable to the test substance.	Mosinger 1965*
Tartaric acid esters	Long-term study: Rats (20 male and 20 female/group) fed diets containing 0, 100 or 400 mg/kg bw/day a substance with 16% tartaric acid ester by weight for 28 months.	No effects observed with food consumption, body weight, food efficiency, reproduction, external appearance, or mortality rate; no effects observed in histological exams attributable to the test substance.	Kieckebusch et al., 1968**

*Unpublished report; results as summarized by JECFA
**Paper published in non-English language; results as summarized by JECFA

Appendix D. PubMed Literature Searches

Date	Search Terms	Citations
10/23/2017	Search ("citric acid" OR citrate) AND infant Sort by: Relevance Filters: Publication date from 2014/01/01 to 2020/12/31	150
10/23/2017	Search (glycerol) AND infant Sort by: Relevance Filters: Publication date from 2014/01/01 to 2020/12/31	58
6/6/2018	Search ("citric acid" OR citrate) AND infant Sort by: Best Match Filters: Publication date from 2017/10/01 to 2020/12/31; English	26
6/6/2018	Search (glycerol) AND infant Sort by: Best Match Filters: Publication date from 2017/10/01 to 2020/12/31; English	4
1/20/2019	Search ("citric acid" OR citrate) AND infant Filters: Publication date from 2018/06/01; English	13
1/20/2019	Search (glycerol) AND infant Filters: Publication date from 2018/06/01; English	7
1/20/2019	Search CITREM OR (citric acid esters) Filters: Publication date from 2014/01/01; English	46

Bonnette, Richard

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Thursday, January 09, 2020 11:47 AM
To: Bonnette, Richard
Cc: Steinborn, Steven B.
Subject: RE: Your recent submissions to the FDA GRAS Notification program (corn oil, citric acid esters of mono and diglycerides, anhydrous milk fat)
Attachments: AMF_Appendix C. Certificates of Analysis on AMF.PDF; AMF_Appendix D. Monitoring for Potential Contaminants.pdf; CITREM Appendix A_Various information - Citrem N 12 Veg MB (093224) Feb....pdf; CITREM Appendix B-1_PAH, Dioxin, Dioxin-like PCBs, Jan. 2017.pdf; CITREM Appendix B-2_2016,Pesticides -Cover letter + Monitoring report (1....pdf; Corn oil_Appendix A.PDF; Corn oil_Appendix B.PDF; Corn oil_Appendix C.PDF; AMF_Appendix A. Analytical Data on AMF.PDF; AMF_Appendix B. Statement of Quality Assurance.pdf

Dear Richard,

Thank you for your note. Here is to confirm the redactions we made all relate to the confidential supplier and customer information, exempt from disclosure under FOIA, and not related to the safety of the GRAS ingredients. Attached, please find the unredacted versions of these pages. For your ease of reference, we also summarize them with the table below:

Document	Page #	Redacted Info
GRAS AMF Appendix A	1, 10, 19	confidential supplier and customer information
GRAS AMF Appendix B	1	confidential supplier and customer information
GRAS AMF Appendix C	1, 2, 3, 4, 5	confidential supplier and customer information
GRAS AMF Appendix D	1, 2, 3, 4	confidential supplier and customer information
GRAS CITREM Appendix A	1, 2	confidential supplier and customer information
GRAS CITREM Appendix B-1	1	confidential supplier and customer information
GRAS CITREM Appendix B-2	1, 2	confidential supplier and customer information
GRAS Corn Oil Appendix A	1, 2	confidential supplier and customer information
GRAS Corn Oil Appendix B	1, 2, 3, 4, 6, 7	confidential supplier and customer information
GRAS Corn Oil Appendix C	1, 2, 3, 4, 5, 6, 7, 8, 9	confidential supplier and customer information

As the above table indicates, all the information we redacted are exempt from disclosure under the Freedom of Information Act, 5 USC 552 as trade secret or as commercial information that is privileged or confidential. They do not

relate to the safety of the ingredients, and we do not view them as basis for our safety conclusions. We also do not view the redacted information as part of the GRAS notices we submitted to the agency.

We trust this is responsive to your request. Please let us know if you have any questions.

Best regards,
Steve
Xin

Xin Tao
Senior Associate

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From: Bonnette, Richard [mailto:Richard.Bonnette@fda.hhs.gov]
Sent: Friday, January 03, 2020 1:24 PM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: Your recent submissions to the FDA GRAS Notification program (corn oil, citric acid esters of mono and diglycerides, anhydrous milk fat)

Dear Mr. Steinborn,
The GRAS submissions for corn oil, citric acid esters of mono and diglycerides, and anhydrous milk fat (all dated November 7, 2019) have completed our prefiling evaluation in the Office of Food Additive Safety. Our pre-filing team here noted that there are minor sections in each of these submissions that are redacted and a non-redacted version was not included. We suspect that these redactions do not obscure safety-relevant information, but will need to see unredacted versions of these sections to make that determination. Can you please provide unredacted versions of these pages that indicate the information that is to be held as exempt from disclosure under FOIA? Also it will be helpful if you provide a brief sentence or two about the nature of the information marked as confidential and why it isn't relevant for safety. You can provide these requested pages by email or by regular mail.

Another option would be to ask us to cease our evaluation of these submissions prior to filing and then resubmit revised versions of these submissions that do not contain redactions.

Let me know if you have any questions.

Regards,
Richard

Richard E. Bonnette, M.S.
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration

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May 1st, 2020

By Electronic Mail

Rachel Morissette, Ph.D.
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

Re: Response to U.S. Food and Drug Administration (FDA)'s Question on Intended Use for GRAS Notices 898, 899, and 900

Dear Dr. Morissette:

In this letter we are responding to the agency's question on the intended use for GRAS Notices 898, 899, and 900 which we submitted for anhydrous milk fat (AMF), citric acid esters of mono- and diglycerides (CITREM), and corn oil's use in exempt infant formulas for "term infants requiring a calorically dense formula and/or fluid restriction." In particular, the agency would like us to *clarify the sub-population of term infants that may consume calorically dense or fluid restrictive infant formula*. This letter supplements the telephone conference we had with the agency on April 24, 2020, and provides a more detailed written narrative of the sub-population that we hope is helpful for the agency's on-going review of GRAS Notices 898, 899, and 900.

Before we address the agency's particular question regarding the sub-population, we first provide a quick overview for the exempt infant formula to which the three ingredients AMF, CITREM, and corn oil will be added. The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increased energy requirements and/or fluid restrictions. The infant formula will be used under medical supervision as a ready-to-feed formulation. CITREM serves as an emulsifier in the formulation, whereas AMF and corn oil are sources of fat that serve as an energy source.

Regarding the particular question from the agency, the sub-populations of infants consuming the formula include the full term infants who are appropriate for oral or enteral feeding, with increased energy and nutrient requirements, fluid restrictions and/or limited ability to take oral feeds. As discussed in the GRAS notices, the nutrient dense formula is a high-energy formulation intended for use in term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism. Full term infants with these special nutritional needs include infants with:

- Congenital heart disease (CHD)
- Chronic lung disease
- Respiratory syncytial virus (RSV)

- Neurological syndrome or neuro-disabilities
- Non-organic cause of growth failure

Among the above medical conditions, we note that certain infants with CHD or chronic lung disease may need to limit their fluid intake to avoid stress to their organs. While we recognize the standards of care for the above medical conditions may differ, all of these are conditions that do not signify altered gastrointestinal function or nutrient metabolism. As such, term infants consuming the calorically dense formula with the three ingredients – AMF, CITREM, and corn oil added would reasonably digest and metabolize them, as do other term infants consuming similarly structured components in human breast milk or standard infant formula.

The sub-population also includes full term infants with cystic fibrosis (CF). While unlike other conditions listed above, CF is a chronic condition with known involvement of the gastrointestinal tract, human milk or standard infant formula is recommended for this infant population under the current standards of care, with pancreatic enzyme supplementation (if indicated). This product would be used under medical supervision.

It is important to note that the formula may not be appropriate for all full term infants requiring a calorically dense formula and/or fluid restriction. Specifically, it is not recommended for conditions including:

- Malabsorption due to causes other than cystic fibrosis,
- Conditions that impact gastrointestinal function or metabolism,
- Significant cow milk protein allergy.

In all, the sub-population of term infants requiring a calorically dense formula and/or fluid restriction that may consume formula containing AMF (GRAS Notice 898), CITREM (GRAS Notice 899), and corn oil (GRAS Notice 900) are term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism and would be expected to handle these three ingredients as would other term infants. The intake of the infant formula will also be under medical supervision.

* * *

If you have any other questions, please do not hesitate to contact us.

Sincerely,

Steve B. Steinborn
steven.steinborn@hoganlovells.com
+1 202-637-5969

Xin Tao
Xin.tao@hoganlovells.com
+1 202-637-6986

Cc:

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Via Electronic Mail

June 11, 2020

Karen M. Hall
Staff Fellow
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
U.S. Food and Drug Administration
Karen.Hall@fda.hhs.gov

Re: Response to FDA's Questions for GRN 000899

Dear Ms. Hall,

We hereby submit our responses to FDA's questions for GRAS Notice 000899 (GRN 899), which covers the intended use of CITREM as an emulsifier in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction.

For your ease of reference, we first copied FDA's questions below, followed by each of our response:

Question #1 (Chemistry):

- ***FDA Question #1****: In the description of the manufacturing process, you state that sodium acetate is used to partially neutralize the product. Please indicate in Figure 2 of your notice where the sodium acetate treatment step takes place.*

Response to Question 1: We have indicated in the revised Figure 2 of GRN 899 where the sodium acetate treatment step takes place. Please refer to **Attachment A** for more details.

Question #2 (Chemistry):

- ***FDA Question #2****: You provide specifications for CITREM that include limits for Enterobacteria. Please provide a specified limit for Cronobacter spp. Specifications for Salmonella and Cronobacter spp. ensure that infant formula products that contain CITREM are in compliance with 21 CFR 106.55.*

Response to Question 2: We recognize the importance of ensuring that infant formulas containing CITREM should be in compliance with 21 CFR 106.55. For powdered infant formula, 21 CFR 106.55(e) provides limits for both *Cronobacter spp.* and *Salmonella* in the finished infant formula product. Because CITREM is an ingredient intended for use in liquid formula only, under 21 CFR 106.55(b), the manufacturer of liquid infant formula shall comply, as appropriate, with the procedures specified in part 113 of this chapter for thermally processed low-acid foods packaged in hermetically sealed containers and part 114 of this chapter for acidified foods. The liquid infant formula manufacturer, who will add CITREM, will have to comply with 21 CFR 106.55 before it can legally market the infant formula in the United States using CITREM. While there is no particular microbial limit under 21 CFR 106.55(b) for ingredients such as CITREM used in manufacturing liquid infant formula, we respectfully submit that our current specifications for CITREM in Table 1 below are sufficient to ensure that the liquid infant formula product can be in compliance with 21 CFR 106.55, and additional microbial limits are unnecessary.

Table 1. Specifications and Methods of Analysis for CITREM

Parameter	Specification	Method of Analysis
Salmonella	absent in 1 g	ISO 6579-1
Enterobacteria	absent in 1 g	ISO 21528-1
Total plate count, CFU/g	Max 5000	3M Aerobic Count Petrifilm Plate 3M 01/01-09/89
Yeast and mold, CFU/g	Max 100	3M Yeast & Mold Petrifilm Plate 3M 01/13-07/14
Abbreviations: CFU – colony-forming units; ISO – International Organization for Standardization;		

Additionally, the highest quality raw materials are used, suitable for use in the manufacturer's specific process that have low contamination rates of microorganisms, as shown in Appendix C. The calorically-dense formula undergoes several processes to ensure all contaminants of concern are eliminated, in particular a wet production process involving a heat treatment (UTH). This heat treatment is 5 seconds at 295°F (146°C), destroying *Cronobacter*, *Salmonella* and other Enterobacteria present. After the UHT treatment, the process is closed and the product is filled aseptically to eliminate chances of product contamination. Additionally, every batch of the final product is tested for commercial stability at 86° F (30°C), which would detect the growth of microorganisms in the exceptional situation they would still be present. We are confident in the

mitigation steps are sufficient from the point of receiving the raw material to producing and shipping of the final product as it relates to controlling for *Cronobacter* and *Salmonella*. Lastly, the production site for CITREM is FSSC 22000 compliant and annual audits are conducted to ensure the highest food safety and ingredient quality.

Question #3 (Chemistry):

- ***FDA Question #3****: For the methods of analysis listed in Table 1 (specifications) of your notice (e.g. GC-method for acids other than citric and fatty acids), we ask that you provide a statement that all methods used are validated for the intended purposes.*

Response to Question 3: We hereby confirm that all methods used in Table 1 are validated for the intended purposes.

Question #4 (Chemistry):

- ***FDA Question #4****: Specified limits for heavy metals in GRN 000899 (Pb ≤2, Cd ≤1, As ≤1.5 & Hg ≤1) exceed those specified in GRN 000511 (Pb ≤1.5, Cd ≤0.1, As ≤0.2 & Hg ≤0.1). You noted in Table 2 (comparison of CITREM specifications) that the JECFA, 2016 specification for lead is ≤ 2 mg/kg for the intended use in foods for the general population. However, this JECFA monograph includes a lead limit of "not more than 0.1 mg/kg for use in infant formula and formula for special medical purposes intended for infants," which more accurately reflects the intended use of CITREM described in your notice. Further, the batch analysis data provided in Table 3 demonstrate that arsenic levels are as high as 1 mg/kg in two of the three batches, which exceed limits described in GRN 000511. Please discuss the appropriateness of the specified limits for heavy metals in CITREM for the intended use in calorically dense, exempt infant formula.*

Response to Question 4: We agree with the agency that when feasible it is important to minimize the presence of heavy metals in the ingredient. GRN 899's heavy metal specifications are based mainly on Food Chemical Codex (FCC), which only lists lead as a potential heavy metal contaminant. We have no reason to believe heavy metals such as cadmium, arsenic or mercury will be present in CITREM. However, in light of the intended use among infant population, and out of an abundance of caution, we have also established CITREM ingredient specifications for cadmium, arsenic and mercury, in addition to lead. Since the submission of GRN 899, in response to FDA's question, and after extensive discussions with our supplier, we have now lowered our specifications for lead and arsenic to 1 mg/kg. These updated specifications are reflected in Table 2 and 3 below (changes highlighted in red).

Table 2. Comparison of Referenced CITREM Specifications

Parameter	JECFA 2016	EU 2008, EU 2012	GRN 511	FCC 11	Current GRAS
Total citric acid, %	13-50	13-50	13-50	13-50	13-50
Total glycerol, %	8-33	8-33	8-33	8-33	8-33
Free glycerol, %	NMT 4	NMT 2	NMT 2	NMT 4	NMT 2
Total fatty acids (as oleic acid), %	37-81	-	37-81	37-81	37-81
Sulfated ash [a] (800±25°C), %	NMT 10	NMT 10	NMT 10	NMT 10	NMT 10
Acids other than citric and fatty, %	-	<1	-	-	<1
Acid value, (mg KOH/g)	-	NMT 130	20-40	-	10-25
Saponification value, (mg KOH/g)	-	-	245-275	-	220-250

Parameter	JECFA 2016	EU 2008, EU 2012	GRN 511	FCC 11	Current GRAS
Lead, mg/kg	NMT 2 [b]	NMT 2	NMT 1.5	NMT 2	NMT 1
Cadmium, mg/kg	-	-	NMT 0.1	-	NMT 1
Arsenic, mg/kg	-	-	NMT 0.2	-	NMT 1
Mercury, mg/kg	-	-	NMT 0.1	-	NMT 1
Salmonella	-	-	ND in 25 g	-	absent in 1 g
Enterobacteria	-	-	NMT 10	-	absent in 1 g
Total plate count, CFU/g	-	-	-	-	Max 5000
Yeast and mold, CFU/g	-	-	-	-	Max 100

CFU – colony-forming units; ND – not detected; NMT – not more than
[a] NMT 0.5% for non-neutralized products, NMT 10% for partially or wholly neutralized products.
[b] Specification for use in foods for the general population.

Table 3. Comparison of Referenced CITREM Specifications

Parameter	Specification	Batch 4012692136	Batch 4012465697	Batch 4013014634
Total citric acid, %	13-50	15	15	15
Total glycerol, %	8-33	25	23	24
Free glycerol, %	NMT 2	1.1	0.8	0.9
Total fatty acids (as oleic acid), %	37-81	- - [a]	- -	- -
Sulfated ash [a] (800±25°C), %	NMT 10	2.3	2.2	2.3
Acids other than citric and fatty, %	<1	Pass	Pass	Pass
Acid value, (mg KOH/g)	10-25	14	14	9
Saponification value, (mg KOH/g)	220-250	240	240	240
Lead, mg/kg	NMT 1	0.4	0.8	0.4
Cadmium, mg/kg	NMT 1	0.1	0.2	0.1
Arsenic, mg/kg	NMT 1	1.0	1.0	0.5
Mercury, mg/kg	NMT 1	0.1	0.1	0.1
Salmonella	absent in 1 g	Pass	Pass	Pass
Enterobacteria	absent in 1 g	Pass	Pass	Pass
Total plate count, CFU/g	Max 5000	100	100	100
Yeast and mold, CFU/g	Max 100	10	10	10

CFU – colony-forming units; NMT – not more than
[a] Controlled via raw materials to be within specifications.

We would also like to clarify heavy metal levels reported in Table 3 of GRN 899 (relevant section copied below) represent detection limits, not the actual levels of the heavy metals detected in CITREM.

Parameter	Batch 4012692136	Batch 4012465697	Batch 4013014634
Lead, mg/kg	<0.4	<0.8	<0.4
Cadmium, mg/kg	<0.1	<0.2	<0.1
Arsenic, mg/kg	<1.0	<1.0	<0.5
Mercury, mg/kg	<0.1	<0.1	<0.1

As the above table indicates, the results should be reported as "non-detected" for all the batches and the numbers used are actually detection limits. Indeed, an additional annual monitoring report (**Attachment B**) provided by the supplier shows the actual levels of these heavy metals can be much lower than the current specifications. In particular, as summarized in **Attachment B**, arsenic is reported to be below 0.1 mg/kg, lead below 0.1 mg/kg, mercury below 0.005 mg/kg and cadmium below 0.01 mg/kg. We note these actual heavy metal levels are either much lower than or comparable to levels in GRN 511. While we acknowledge the current specifications are set higher than levels reported in the monitoring program, there is a consistent effort by the supplier to continue to lower the detection levels for these heavy metals based on the most recent analytical methods developed.

Further, to support the appropriateness of the specified limits for heavy metals in CITREM for the intended use in calorically dense, exempt infant formula, we have also calculated the maximum levels of heavy metals in infant formula that could be introduced by CITREM. As the maximum use level of CITREM indicated in GRN 899 is 233 mg/100 mL, and assuming the typical infant formula has a density of 1.05 g/mL and the CITREM ingredient contains the heavy metal contaminants at levels up to the specifications, the maximum levels of heavy metals in this exempt infant formula can be summarized below:

Parameter	CITREM Specification	Infant Formula Theoretical Maximum Level from CITREM
Lead, mg/kg	1	2.22 ppb 1/
Cadmium, mg/kg	1	2.22 ppb
Arsenic, mg/kg	1	2.22 ppb
Mercury, mg/kg	1	2.22 ppb

1/ 2.22 ppb = 1 mg/kg x (233 mg/(100mL x 1.05 g/mL) x 1,000 ppb/ppm.

When we set the specifications, we reviewed the EU Commission Regulation (EC) No 1881/2006 where the lead and cadmium limits in liquid infant formula are provided as 10 ppb and 5 ppb respectively. While no limit was provided for mercury or arsenic, the lowest (EC) No 1881/2006 limits on mercury is 100 ppb in food supplements, which is much higher than the theoretical 2.22 ppb. As for arsenic, because the theoretical level of 2.22 ppb is magnitude lower than the 100 ppb FDA action level for inorganic arsenic in infant rice cereals, 2/ we respectfully submit our current specification that may result in a theoretical maximum level of 2.22 ppb in infant formula from the intended use does not pose any safety concern.

2/ FDA, Inorganic Arsenic in Rice Cereals for Infants: Action Level Guidance for Industry (April 2016), *available at*: https://www.fda.gov/media/97234/download.

Question #5 (Chemistry):

For estimates of infant formula consumption, the maximum intake described in your notice is based on the "highest achieved formula intake" level of 175 kcal/kg bw/d from a published study (Clarke et al., 2007) in which the targeted intake was up to 200 kcal/kg bw/d.

- ***FDA Question #5a****: Please address whether this level of caloric intake (175 kcal/kg bw/d) is reasonable and/or sustainable in the subpopulations that would consume calorically-dense formula. We note that, while 175 kcal/kg bw/d or even 200 kcal/kg bw/d may be useful in describing the upper range of possible intakes, this level does not appear to be a reasonable estimate of the 90th percentile of exposure. We note that we have seen pseudo-90th percentile dietary exposures for infant formula ingredients calculated assuming the 90th percentile dietary exposure is approximately 1.2x the mean dietary exposure. Based on a 1.2x approach and the mean intake of 120 kcal/kg bw/d cited in the notice, the 90th percentile would be 144 kcal/kg bw/d. This value is close to the cited value of 141.3 kcal/kg bw/d from Fomon (1993) for male infants 14-27 days of age.*

Response to Question 5a: As there are currently no similar products in the US market today, the estimates of dietary exposure presented in the GRAS notification correspond to the mean level of intake of a calorically dense infant formula achieved across several clinical studies (i.e., 120 kcal/kg bw/day) and the highest achieved formula intake per 24 h in a 6-week intervention (i.e., 175 kcal/kg bw, as cited in Clarke et al., 2007). These levels of formula intake were designated in the GRAS notification as representative of typical and high formula intake, respectively. The level of "high" intake identified in the notification provides a conservatively high estimate for the purpose of a safety assessment and may be achieved by some infants as reported in the referenced clinical trial but is not necessarily a level representative of a 90th percentile intake. The actual representative 90th percentile intake could be lower than the 175 kcal/kg bw/day. We also note the exempt infant formula will be administered under the supervision of doctors, and the use will necessarily vary depending on the infant conditions and duration needed. However, by using the 175 kcal/kg bw/day during our dietary exposure assessment, we are able to establish the intended use to be safe with an extra level of conservatism.

- ***FDA Question #5b****: We request that you provide mean and 90th percentile exposure estimates for infants less than 6 months of age and for older infants 6-12 months of age based on reference data for caloric needs of the subpopulation(s) of infants consuming energy-dense formulas. Caloric needs may be based on published estimates of energy needs for catch up growth or other reference data as supported by the discussion. Regardless of the approach, please address what level approximates a reasonable estimate of 90th percentile exposure estimates for infants consuming these ingredients*

Response to Question 5b: Published estimates of recommended energy intakes, in particular recommended intakes for infants with elevated nutrient requirements to address faltering growth, provide an alternate approach for estimating formula intake by the target population of infants that may consume the calorically dense infant formula. Guidance for care of critically ill pediatric patients recommends use of a predictive equation such as the Schofield equation to estimate nutrient needs (Mehta et al., 2017). The Schofield equation provides a basis to calculate resting energy requirements with a stress factor to adjust for an infant's particular needs. The equations for male and female infants to 3 years of age are as follows (weight in kg, height in cm):

Male: (0.167 x weight) + (15.174 x height) – 617.6

Female: (16.252 x weight) + (10.232 x height) – 413.5

The resulting estimate of resting energy requirements is then multiplied by a stress factor corresponding to an infant's condition:

Table 4. Schofield Stress Factors

Fever	12% per degree >37C
Cardiac Failure	1.15 – 1.25
Major Surgery	1.2 – 1.3
Sepsis	1.4 – 1.5
Catch-up growth	1.5 – 2
Burns	1.5 - 2

Using a median height for male infants ages 1 to 12 months and assuming a weight at the 3rd percentile to represent an infant at risk for growth faltering, the estimated energy needs based on the Schofield equation and a range of stress factors representative of conditions infants consuming a calorically dense formula may experience are summarized in Table 2. The stress factors selected for these calculations include 1.25, which corresponds to the midpoint of infants undergoing surgery (and the upper end of the range for infants with cardiac failure), and factors of 1,5, 1.75, and 2.0, which correspond to the lower bound, midpoint, and upper bound of the recommended range for catch-up growth of 1.5-2.0.

Table 5. Estimated energy requirements for male infants with stress factors for surgery and catch-up growth

Age (months)	Reference height (cm, 50th percentile)	Reference weight (kg, 3rd percentile)	Basal Energy Requirement kcal/day	Energy Requirement by Stress Factor kcal/kg bw/day			
				1.25	1.5	1.75	2.0
1	54.7	3.2	213	83	100	116	133
2	58.1	4.0	265	83	99	116	132

3	60.8	4.7	306	81	98	114	130
4	63.1	5.3	341	80	96	113	129
5	65.2	5.8	373	80	96	112	129
6	67	6.3	400	79	95	111	127
7	68.7	6.8	426	78	94	110	125
8	70.2	7.2	449	78	94	109	125
9	71.6	7.5	470	78	94	110	125
10	73	7.8	491	79	95	110	126
11	74.3	8.1	511	79	95	110	126
12	75.5	8.4	529	79	95	110	126

Body weight and height for infants, IOM, 2005 (based on CDC Growth Charts: United States. National Center for Chronic Disease Prevention and Health Promotion, 2000).

For infants ages 1 to 6 months, the highest estimated energy requirement at the midpoint for catch-up group is 116 kcal/kg bw/day, which is similar to the reported intakes of approximately 120 kcal/kg bw/day from the clinical studies. The Institute of Medicine (IOM) identifies the reference energy needs for catch-up growth at 113 to 123 kcal/kg bw/day assuming a rate of gain of 10 g/kg bw/day in children, which likewise is consistent with values calculated with the Schofield equation (IOM, 2005; Table 5-32). The value also is consistent with mean formula intake for formula-fed infants with the highest intake per kg bw as reported by Fomon (1993), namely 121.1 kcal/kg bw/day for boys age 14-27 days. Collectively, energy intakes as reported in clinical trials of infants consuming calorically dense formula and estimated energy needs for infants who may be recommended for use of the formula suggest that intake of 120 kcal/kg bw/day is representative of mean energy intake for the target population of infants up to 6 months of age.

Assuming a factor of 1.2 times the mean intake for a pseudo-90th percentile intake, the pseudo-90th percentile intake by infants with a mean energy intake of 120 kcal/kg bw/day is 144 kcal/kg bw/day. This pseudo-90th percentile intake is close to the cited value of 141.3 kcal/kg bw/d from Fomon (1993) for 90th percentile intake by male infants 14-27 days of age.

The estimated mean energy needs for infants age 6-12 month requiring catch-up growth is approximately 110 kcal/kg bw/day assuming a stress factor corresponding to the midpoint of the range for catch-up growth (Table 2), which is slightly lower than the estimated needs for catch-up growth for an infant in the first 6 months of life. Assuming a mean energy intake of 110 kcal/kg bw/day, the pseudo-90th percentile intake is 132 kcal/kg bw/day for infants 6-12 months of age assuming a factor of 1.2 times the mean intake for a pseudo-90th percentile intake.

Multiplying the energy intake discussed above with the maximum proposed use level of CITREM in the calorically dense infant formula (100 kcal/mL), we calculated the estimated daily intake of CITREM below:

Table 6. Estimated Daily Intake of CITREM from the Maximum Proposed Use

Calorically Dense Formula Intake		CITREM
Population and intake	kcal/kg bw/day	mg/kg bw/day
Infants 0-6 months		
Typical	120	280
Pseudo-90th percentile	144	336
Infants 6-12 months		
Typical	110	256
Pseudo-90th percentile	132	308

Assumptions: 100 kcal per 100 mL; 233 mg CITREM per 100 mL

Question #6 (Toxicology):

- ***FDA Question #6****: 3-Monochloropropane-1,2-diol esters (3-MCPDE) and glycidyl esters (GE) are chemical contaminants formed during the refining process of edible oils and which have been identified in infant formula. Due to their toxicological properties, JECFA established a PMTDI for 3-MCPD and 3-MCPD esters of 4 µg/kg body weight per day2 and EFSA derived a TDI of 2 µg/kg body weight per day for 3-MCPD and its esters.3 JECFA and EFSA have reviewed GE and consider glycidol to be a potential genotoxic carcinogen. The manufacture of CITREM includes the use of a refined, hydrogenated palm oil that is described as food grade. Given the stated toxicity concerns and recent efforts to reduce exposure to 3-MCPDE and GE in infant formula from refined oils, please discuss (1) the potential presence of these contaminants in hydrogenated palm oil and CITREM, and (2) if these contaminants are present, please provide a narrative that supports the safe use of CITREM in the intended infant population. A discussion of mitigation strategies can be found in the Codex Code of Practice entitled "Reduction of 3-monochloropropane-1,2-diol esters (3-MCPDE) and glycidyl esters (GE) in Refined Oils and Food Products Made with Refined Oils" (adopted July 2019, 42nd session, Codex Alimentarius Commission).*

Response to Question 6: Regarding the agency's question (1) the potential presence of 3-MCPDE and GE in hydrogenated palm oil and CITREM, we acknowledge the exposure to these contaminants can occur through consumption of CITREM. 3-MCPDE can be present in most vegetable oils and fats (in particular palm oils). On the other hand, GE can be formed from a group of substances that are naturally present in all vegetable oils when they are heated to temperatures > 200 °C. The supplier has looked into and implemented proprietary measures in line with those discussed in the Codex Code of Practice (CoP) the agency referenced and entitled "Reduction of 3-monochloropropane-1,2-diol esters (3-MCPDE) and glycidyl esters (GE) in Refined Oils and Food Products Made with Refined Oils" (adopted July 2019, 42nd session, Codex Alimentarius Commission) to further mitigate the formation of these impurities. The supplier will continue to look into additional mitigation measures to further reduce their formation as our knowledge with these impurities continues to evolve and in the meantime the levels of 3-MCPDE and GE are closely monitored and levels follow the applicable EU regulations.

Regarding the agency's question (2) if these contaminants are present, please provide a narrative that supports the safe use of CITREM in the calorically dense exempt infant formula referenced in GRN 899. The supplier has established maximum limits for GE at 1 mg/kg in CITREM and 3-MCPDE at 1.25 mg/kg in CITREM. Further, the level of chemical contaminants in the exempt infant formula follow EU regulations, which include EU Commission Regulation (EC) 2018/290 denoting a max 6 ppb for GE in products intended for infants and young children. In addition, a 3-MCPDE max limit of 15 ppb is followed per the recently amended EU Commission Regulation (EC) No 1881/2006, which dictates a maximum level of 15 ppb for 3-MCPDE in infant formula and other products intended for young children. As the finished

product meets the applicable international standards (i.e., EU regulations) for 3-MCPDE and GE impurity levels for uses in infant population, we respectfully submit CITREM under GRN 899 can be used as intended.

It is also relevant to note that the total amount of CITREM in the finished good is less than 1% of the total formula, resulting in a very small amount of contaminants in the final product. Below, we conducted a quick risk assessment using the TDI developed by JECFA for 3-MCPDE.

Assuming a pseudo-90th percentile formula intake of 144 kcal/kg bw/day as discussed in Question 5 above and the proposed maximum use of CITREM of 233 mg CITREM per 100 mL, the maximum concentration of 3-MCPDE and its esters that can be present in the ingredient to provide an exposure of no more than 2 µg/kg bw/day is 6 mg/kg.

The calculation is shown below:

$$\frac{233\ mg\ CITREM}{100\ ml}\ X\ \frac{100\ mL}{100\ kcal}\ X\ \frac{144\ kcal}{kg\ bw/day}\ X\ \frac{\boldsymbol{MAX}\ mcg\ 3MCPDE\ \dagger}{mg\ CITREM} = \frac{2\ mcg\ 3MCPDE}{kg\ bw/day}$$

$$\boldsymbol{MAX} = \frac{6\ mg}{kg\ CITREM}$$

†*and its esters*

As the CITREM ingredient contains 3-MCPDE at the maximum level of 1.25 mg/kg, which is much smaller than 6 mg/kg, we concur that 3-MCPDE in CITREM does not pose any safety concern from the intended use.

Question #7 (Toxicology):

- ***FDA Question #7****: In your supplemental letter (dated May 1, 2020) that provided information on the subpopulation of term infants intended to consume your calorically dense or fluid restrictive infant formula, you indicate that the "current standard of care" recommended for infants with cystic fibrosis (CF) is "human milk or standard formula…with pancreatic enzyme supplement (if indicated)" (emphasis added). This statement appears to suggest the use of typical, non-exempt infant formula in infants with CF. Please clarify and explain the intended use of your exempt, calorically dense infant formula in CF infants. Also, please briefly discuss the safety of the intended use of your ingredient, CITREM, in a calorically dense formula (i.e., expected to provide more fat per feeding) considering the gastrointestinal abnormalities often found in infants with CF.*

Response to Question 7: The current standard of care recommended for feeding infants with CF is to use human milk or standard infant formula with pancreatic enzyme supplementation (if indicated). 3/ For infants with CF who demonstrate weight loss or inadequate weight gain, calorie-dense feedings are recommended. 4/

Currently, in the United States, these infants with CF who are indicated for feeding with a calorically-dense infant formula would be fed a standard (non-exempt) infant formula prepared at a higher caloric concentration (i.e. higher ratio of powder or liquid concentrate to water than standard directions by the manufacturer to prepare the infant formula at standard caloric concentration of 65 – 67kcal/ml) in order to achieve the higher caloric density recommended. This would be done at the direction of the infant's health care team (i.e. as directed by physician or dietitian).

Standard (non-exempt) infant formulas typically provide 48-50% of calories from fat. When prepared at a higher caloric density, the percent energy from fat remains constant at 48-50%. The calorically-dense infant formula described in this GRAS will provide 48-50% with kcal from fat not to exceed 50%. Therefore, the fat load will be comparable to what is provided when following the current practice; use of the calorically dense formula will not provide more fat per feeding than the current practice of concentrating a standard formula.

As described by Wouthuyzen-Bakker et al., 2011, CF impacts the gastrointestinal system and high energy diets and pancreatic enzyme replacement therapy (PERT) are typical parts of treatment throughout the patient's lifespan. Nonetheless, in infants with CF, specialized

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3/ Cystic Fibrosis F, Borowitz D, Robinson KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *The Journal of pediatrics.* 2009;155(6 Suppl):S73-93.

4/ *See id*.

hydrolyzed formulas have not been shown to confer improved nutrition or health benefits and the Cystic Fibrosis Foundation continues to recommend that when infant formulas are used, standard infant formulas should be used (in conjunction with PERT if indicated). Furthermore, if inadequate growth or weight gain is observed, increasing caloric density of feedings is recommended. In cases where a calorie-dense feeding is recommended, the fat load of feeding with the calorie-dense formula described in this GRAS will be comparable to calorie-dense feedings with standard infant formula and therefore, would not be expected to be tolerated differently than the current practice. As always, this formula should only be used under medical supervision.

Formula Type	Caloric Density	Percent Calories from Fat
Standard Infant Formula	65 – 67 kcal/100 ml	48 – 50% of calories from fat
Calorically – Dense Formula	100 kcal/100 ml	<50% of calories from fat

As noted in GRN 899, CITREM is likely to be substantially hydrolyzed in the gastrointestinal tract into its component elements of citric acid (or a related organic acid), free fatty acids, and glycerol, or partially hydrolyzed products such as glycerol citric acid esters that would not present a safety concern. For infants with CF who have gastrointestinal abnormalities, high energy diets and pancreatic enzyme replacement therapy are recommended. When consumed by an infant with CF, the CITREM component within the energy dense formula can reasonably be assumed to be hydrolyzed into common dietary components as are other fats. As noted above, the fat load provided by the energy dense formula will be comparable to what is provided in current practice.

CITREM is currently recognized as GRAS for use in exempt amino-acid based and hydrolyzed formulas at a level of 233 mg CITREM per 100 mL as detailed in GRN 511. The use level of CITREM in GRN 511 is identical to the proposed use level of CITREM in this GRAS notice on a 100 mL basis. Amino-acid based and hydrolyzed formulas are formulas recognized to serve the needs of infants with a range of digestive conditions, including but not limited to malabsorption disorders, intractable diarrhea, short gut, milk allergy, and potentially cystic fibrosis among other conditions.[5] The use of CITREM at a level of 233 mg CITREM per 100 mL in formula for infants with gastrointestinal abnormalities therefore has previously been recognized as safe (GRN 511).

5/ Green Corkins K, Shurley T. What's in the Bottle? A Review of Infant Formulas. Nutr Clin Pract. 2016 Dec;31(6):723-729.

As reviewed in GRN 899 and below in Question #8, based on the intended use of CITREM, CITREM is safe and GRAS based on the totality of data and information provided in the GRAS notice.

Question #8 (Toxicology):

- ***FDA Question #8****: On page 30 of the GRAS notice, you state "JECFA established an ADI of "not specified" for citrate (JECFA, 1974)…" However, page 65 of the report of the seventy-ninth meeting of JECFA8 states that "Citric acid has been evaluated previously by the Committee…and given an ADI "not limited" [A term no longer used by JECFA that has the same meaning as ADI "not specified"], but this evaluation did not cover infants less than 12 weeks of age" (emphasis added). Please clarify the statement in the GRAS notice and provide a comment as to whether this information alters your safety conclusion regarding citric acid in the intended infant population.*

Response to Question 8: We apologize for any confusion. JECFA evaluated citric acid and assigned an ADI "not limited", which has the same meaning as ADI "not specified". As the agency pointed out, JECFA's evaluation *did not cover infants less than 12 weeks of age*. However, this information does not alter the safety conclusion presented in the GRN 899. As noted in the GRAS notification, citric acid has a well-established role as an intermediate metabolite in the tricarboxylic acid cycle (TCA) and is a normal metabolite in the body. The safety assessment of the proposed use of CITREM includes discussion of citrates in human milk, infant formulas, and weaning foods. As part of the safety assessment, potential gastrointestinal effects of citric acid were reviewed. The available limited evidence indicates that adverse effects of diarrhea are possible with citric acid intake in excess of 400 mg/kg bw/day, though in one study no adverse gastrointestinal effects were observed with intake of approximately 500 mg/kg bw/day citrate salts. The observed occurrence of diarrhea in some studies may in part be an artifact of the bolus exposures that are not representative of formula intake by infants.

Assuming a pseudo-90th percentile formula intake of 144 kcal/kg bw/day as discussed in Question 5 above, the proposed maximum use of CITREM and citric acid from other ingredients typical in infant formula and the maximum permitted concentration of citric acid in CITREM (i.e., 50%) is estimated at 260 mg citric acid per kg bw/day. This level of citric acid intake is well below the range associated with diarrhea and therefore does not present a safety concern. As such, we do not expect the intended use to pose any safety concern even for infants less than 12 weeks of age.

Table 7. REVISED Estimated Intake of CITREM and Citric Acid from the Maximum Proposed Use of CITREM

Energy Dense Formula[a]	CITREM (mg/kg bw/day)	Citric Acid (mg/kg bw/day)

Intake	kcal/kg bw/day	Maximum of 233 mg/100 mL	Typical from CITREM (15%)	Maximum from CITREM (50%)	Back-ground from formula[b]	Typical TOTAL	Maximum TOTAL
Typical	120	280	42	140	77	119	217
High	144	336	50	168	92	142	260

[a]Assume 100 kcal per 100 mL

[b] 64 mg citric acid per 100 mL in infant formula based on a mean concentration of 3.34 mmol/L citrate and a molecular weight of 192.124 g/L for citric acid (FAO/WHO 2015; Hoppe et al., 1998).

Question #9 (Infant Formula and Medical Foods Questions):

- ***FDA Question #9****: Please clarify the intended source of the protein base (ex. milk, soy, whey) of infant formula that the ingredient would be added into.*

Response to Question 9: This formula is milk-based (blend of whey and casein) in order to provide the most optimal amino acid profile.

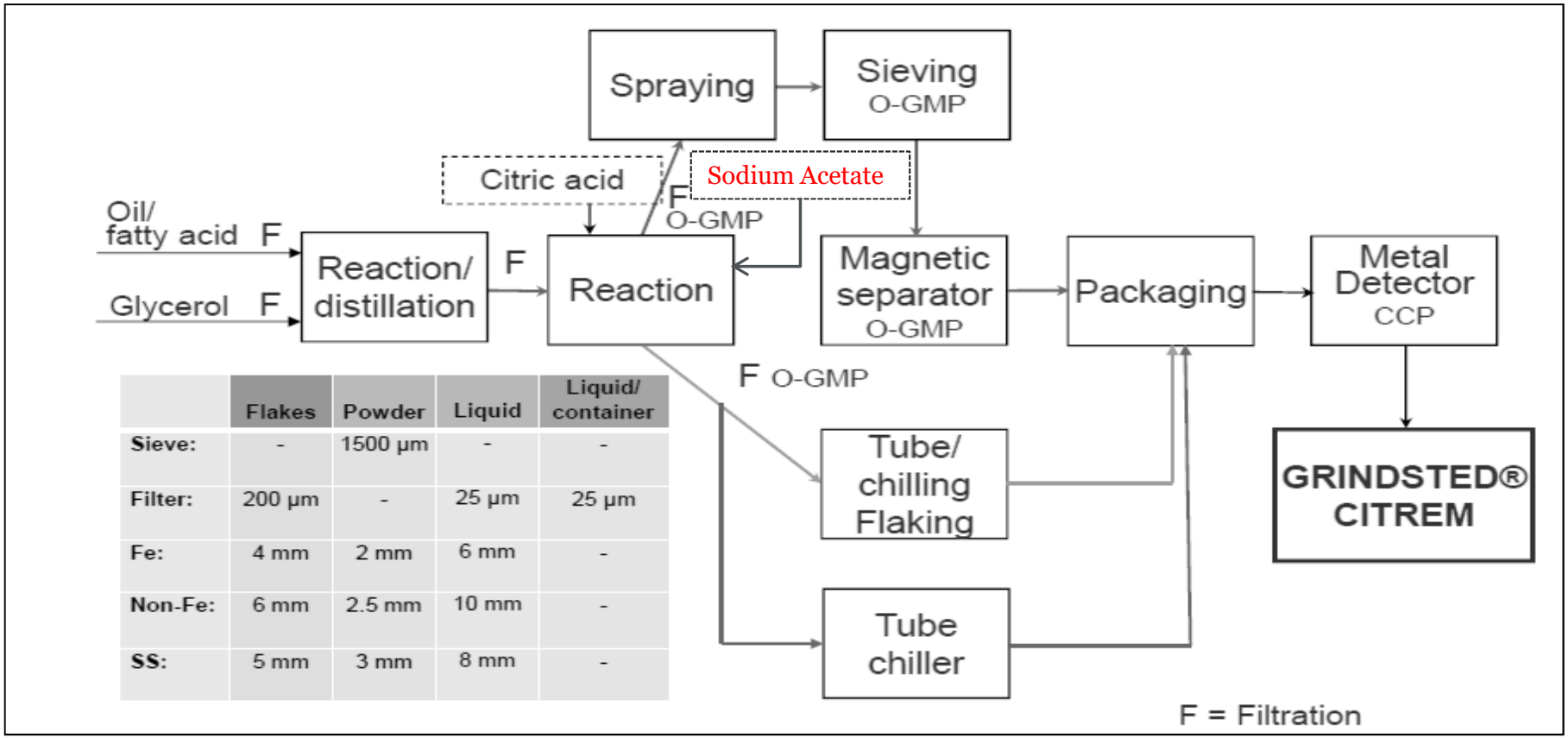
* * *

If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

Steven B. Steinborn
Partner
Hogan Lovells US LLP
steven.steinborn@hoganlovells.com
202 637 5969

Revised Figure 2 of GRN 899



	Flakes	Powder	Liquid	Liquid/ container
Sieve:	-	1500 µm	-	-
Filter:	200 µm	-	25 µm	25 µm
Fe:	4 mm	2 mm	6 mm	-
Non-Fe:	6 mm	2.5 mm	10 mm	-
SS:	5 mm	3 mm	8 mm	-

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Via Electronic Mail

September 24, 2020

Karen M. Hall
Staff Fellow
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
U.S. Food and Drug Administration
Karen.Hall@fda.hhs.go

Re: Response to FDA's Follow-up Question for GRN 000899

Dear Ms. Hall,

We hereby submit our responses to FDA's follow-up question for GRAS Notice 000899 (GRN 899). For your ease of reference, we first copied FDA's questions below, followed by our response:

- ***FDA Question #1: In Table 2 of the notice (page 12), you compare your specifications with those of GRN 000511. We note that the specification for Salmonella serovars in GRN 000511 is ND in 25 g, while the specification for Salmonella serovars in your notice is absent in 1 g. For the administrative record, please explain this discrepancy in the sample size.***

Hogan Lovells Response: At the outset, we would like to note that as discussed in the notice, specifications established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Union (EU), the Food Chemicals Codex (FCC) do not have a microbial limit for *Salmonella* for the food ingredient CITREM. In GRN 511, the notifier has established a limit for *Salmonella* at "absence in 25 g." However, no reference to analytical test method was provided in GRN 511 for this limit. Our limit of "absence in 1 g" is based on batch data generated with ISO 6579-1 by our supplier. We suspect the difference could be due to the different test methods used, but without knowing the test method used by GRN 511, we are not able to make that comparison.

Further, the infant formula manufacturer, who will add CITREM, will have to comply with 21 CFR 106.55 before it can legally market the infant formula in the United States using CITREM. While there is no particular microbial limit under 21 CFR 106.55 for ingredients such as CITREM, we respectfully submit that our current specification for *Salmonella* in CITREM "absence in 1 g" is

sufficient to ensure that the infant formula product can be in compliance with 21 CFR 106.55, and additional microbial limits are unnecessary.

- ***FDA Question #2: In your response, you state that the method used to detect Enterobacteria is ISO 21528-1, which corresponds to Microbiology of Food Chain – Horizontal Method for the Detection and Enumeration of the Enterobacteriaceae – Part 1: Detection of Enterobacteriaceae. We note that references to "Enterobacteria" on pages 12-13 and in Appendix A of the notice; and in answers to questions 2 and 4 of the June 11, 2020 amendment should read "Enterobacteriaceae". For the administrative record, please provide a statement that you agree.***

Hogan Lovells Response: We agree. We hereby confirm the correct term we should have used is "Enterobacteriaceae" instead of "Enterobacteria" as the agency noted. We apologize for any confusion.

* * *

If any additional questions arise in the course of your review, please contact us, preferably by telephone or e-mail, so that we can provide a prompt response.

Sincerely,

Steven B. Steinborn
steven.steinborn@hoganlovells.com
202 637 5969

From:	Tao, Xin
To:	Morissette, Rachel; Steinborn, Steven B.
Cc:	Harry, Molly; Hall, Karen
Subject:	RE: additional questions for GRNs 000898, 000899, 000900
Date:	Wednesday, October 21, 2020 12:02:39 PM
Attachments:	image001.png

Dear Rachel, Molly, and Karen,

Please see our response to the additional questions below.

1. *In your response dated May 1, 2020, you stated the following:*

"The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increase energy requirements and/or fluid restrictions."

We note that "infants" are defined as 0-12 months of age. Thus, it is not clear whether your intended use for infants/toddlers aged 12-18 months is in the form of infant formula or other types of formula. We suspect that the 12-18 months subpopulation weighing less than 9 kg as a part of your intended use likely includes infants suffering from a particular affliction that would necessitate feeding infant formula. Please briefly and clearly explain your use for toddlers aged 12-18 months.

HL Response: we hereby clarify GRNs 898, 899, and 900 only cover the intended uses of the ingredients in exempt infant formula for infants (i.e., 0-12 months).

2. *Please confirm that the intended use in GRNs 000898, 000899, and 000900 does not include non-exempt infant formula or any other types of exempt formula not specified in the notice.*

HL Response: we hereby confirm the intended use in GRNs 898, 899, and 900 does not include non-exempt infant formula. The intended uses are for the ingredients to be used in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction as specified in the notices.

We trust we are responsive to the questions, and please let us know if the agency has any further questions.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

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From: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Sent: Thursday, October 15, 2020 3:46 PM
To: Tao, Xin <xin.tao@hoganlovells.com>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Cc: Harry, Molly <Molly.Harry@fda.hhs.gov>; Hall, Karen <Karen.Hall@fda.hhs.gov>
Subject: additional questions for GRNs 000898, 000899, 000900

Dear Xin and Steve,

We have two additional clarification questions regarding the intended use in these three notices. Please provide a response as soon as possible, within 5 business days, to facilitate the completion of our review of these notices.

1. *In your response dated May 1, 2020, you stated the following:*

   "The infant formula is a nutritionally complete and nutrient dense formula intended for use among full-term infants from birth and up to 18 months of age (or 9 kg) with increase energy requirements and/or fluid restrictions."

   We note that "infants" are defined as 0-12 months of age. Thus, it is not clear whether your intended use for infants/toddlers aged 12-18 months is in the form of infant formula or other types of formula. We suspect that the 12-18 months subpopulation weighing less than 9 kg as a part of your intended use likely includes infants suffering from a particular affliction that would necessitate feeding infant formula. Please briefly and clearly explain your use for toddlers aged 12-18 months.

2. *Please confirm that the intended use in GRNs 000898, 000899, and 000900 does not include non-exempt infant formula or any other types of exempt formula not specified in the notice.*

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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If you would like to know more about how we are managing the impact of the COVID-19 pandemic on our firm then take a look at our brief Q&A. If you would like to know more about how to handle the COVID-19 issues facing your business then take a look at our information hub.

About Hogan Lovells
Hogan Lovells is an international legal practice that includes Hogan Lovells US LLP and Hogan Lovells International LLP. For more information, see www.hoganlovells.com.