#900

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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 Corn Oil in Exempt Infant Formula

Dear Sir or Madam:

We hereby submit the enclosed GRAS notice for Corn Oil as an ingredient in exempt infant formula. Corn oil is intended for use as a source of fat in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction. The maximum intended use of corn oil in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is 3.0 percent of the fat blend by weight. Hogan Lovells US LLP's conclusion of GRAS status for the intended use of corn oil in exempt infant formula is based on scientific procedures in accord with 21 CFR §170.30(a) and (b).

Corn oil 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

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

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

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000900	Jan 09 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

SECTION C – GENERAL ADMINISTRATIVE INFORMATION

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

Corn oil

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.

Corn oil is intended for use as a source of fat in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction. The maximum intended use of corn oil in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is 3.0 percent of the fat blen

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

☐ ☐

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

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

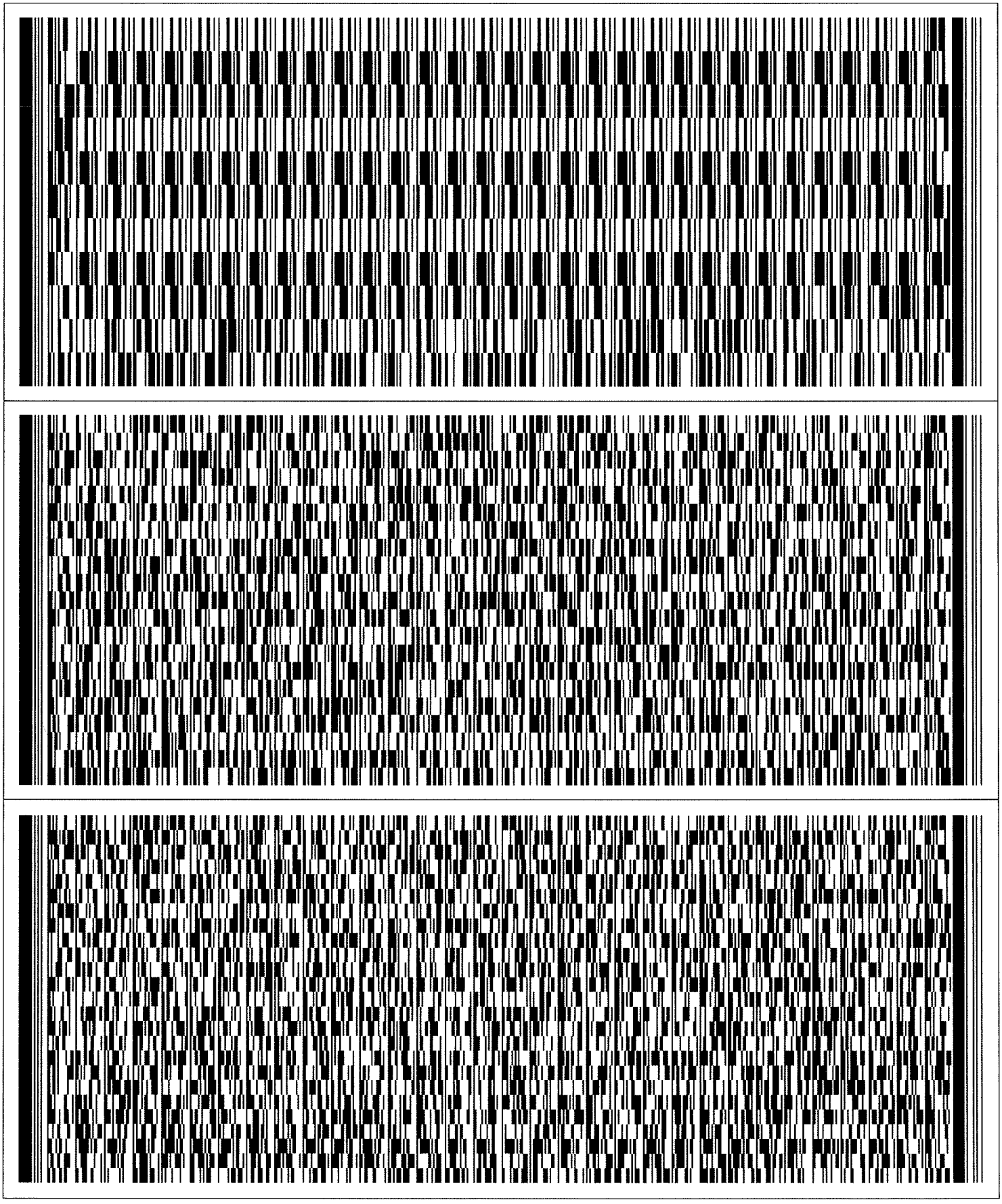
The notifying party certifies that this GRAS notice is a complete, representative, and balanced submission that includes unfavorable, as well as favorable information, pertinent to the evaluation of the safety and GRAS status of the use of the substance.The notifying party certifies that the information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

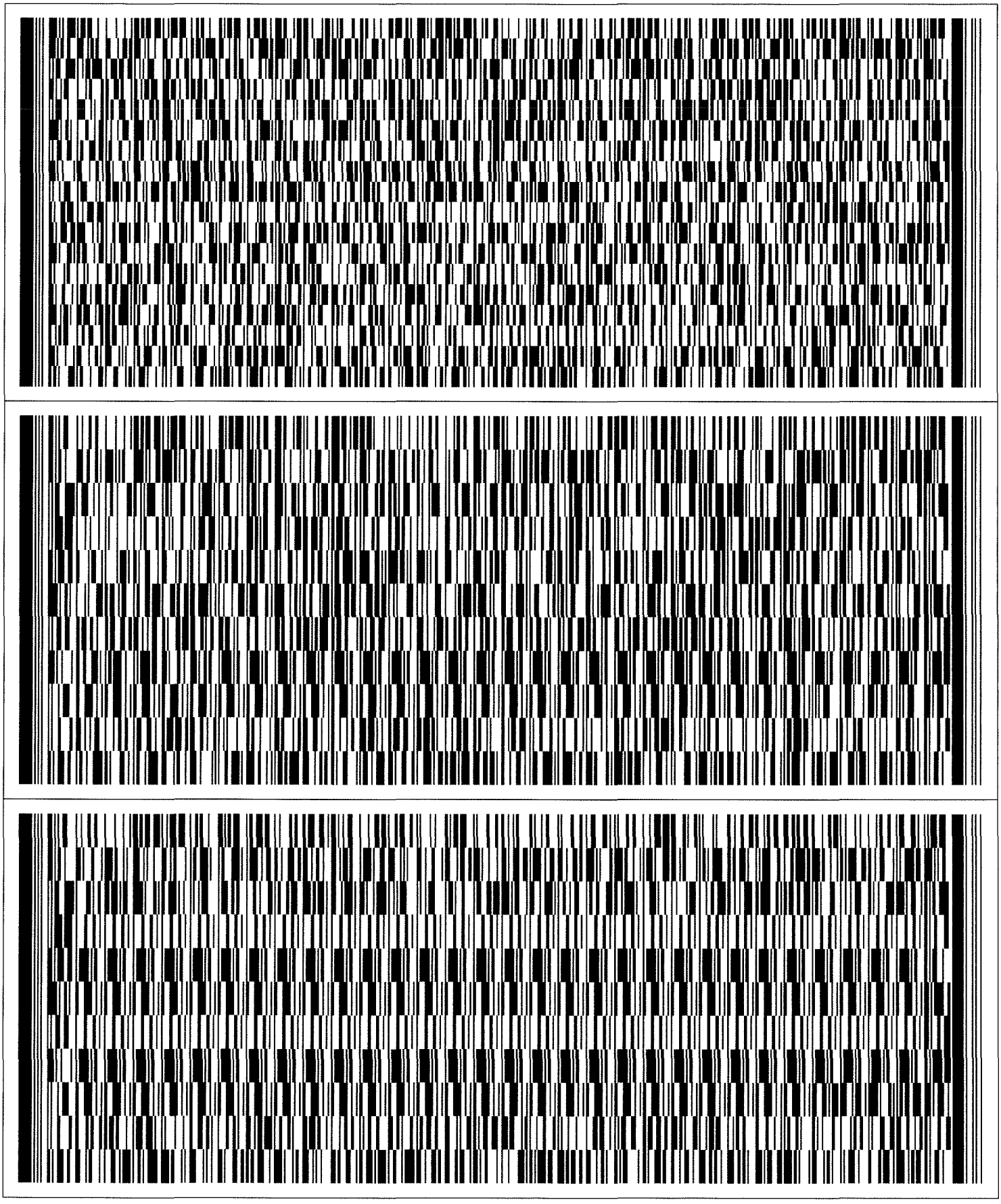
3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
	Steven Steinborn	11/06/2019

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. Food Safety and Quality Assurances	Submission
	Appendix B. Analytical Data	Submission
	Appendix C. Contaminant Specifications and Analytical Data	Submission
	Appendix D. PubMed Literature Searches	Submission





GRAS Conclusion for the Use of Corn Oil in Exempt Infant Formula

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

Table of Contents

List of Tables

List of Figures

List of Acronyms

ADI	acceptable daily intake
bw	body weight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
d	day
DHA	docosahexaenoic acid
EDI	Estimated Daily Intake
EFSA	European Food Safety Authority
F	female
FAO	Food and Agriculture Organization
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
FOIA	Freedom of Information Act
g	gram
GRAS	Generally Recognized As Safe
GRN	GRAS Notice
h	hour
JECFA	Joint Expert Committee on Food Additives
kcal	kilocalorie
kg	kilogram
LA	linoleic acid
LSRO	Life Sciences Research Office
M	male
mg	milligram
mL	milliliter
n	number
NA	not applicable
ND	not detected
PAH	polyaromatic hydrocarbons
PCB	polychlorinated biphenyl
ppm	parts per million
RCT	randomized controlled trial
U.S.	United States
USDA	U.S. Department of Agriculture
WHO	World Health Organization
wk	week

y	year
µg	microgram

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 corn oil.

Intended Use and Consumer Exposure

Corn oil is intended for use as a source of fat in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction. The maximum intended use of corn oil in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is 3.0 percent of the fat blend by weight.

Basis for Conclusion of GRAS Status

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

Pre-Market Approval Exclusion Claim

The intended use of corn oil in exempt infant formula 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 generally recognized as safe (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's office located at:

555 13th St NW

Washington, DC 20004

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 of this dossier is corn oil, which is also known as maize oil.

Chemical Abstracts Services (CAS) Registry Number

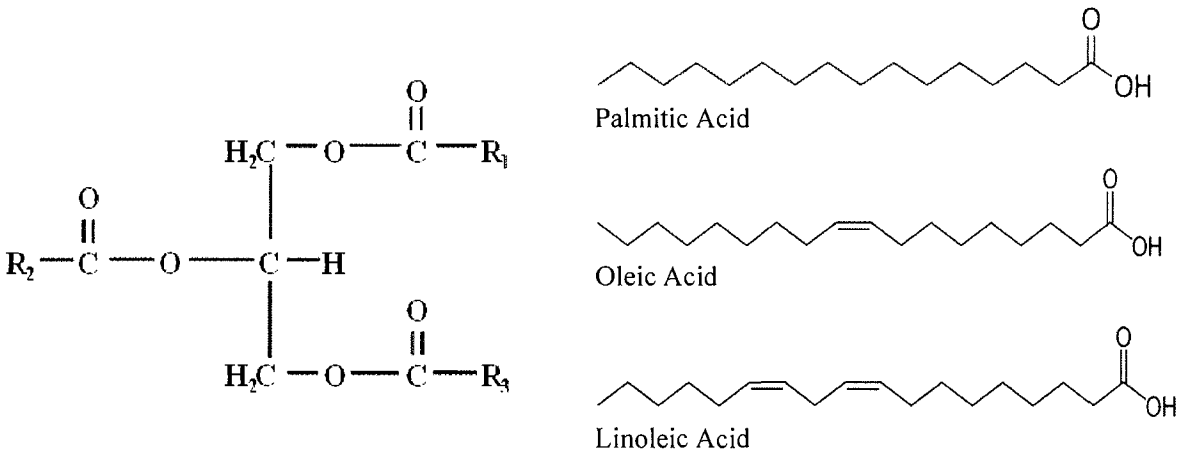
The Chemical Abstracts Service (CAS) registry number for corn oil is 8001-30-7.

Composition of Corn Oil

Fatty Acids

Corn oil is a mixture of triglycerides composed of both saturated and unsaturated fatty acids, of which the major fatty acid components are linoleic, oleic, and palmitic fatty acids. The typical structure of corn oil, including the structure of the major fatty acids, is shown in Figure 1.

Figure 1. Typical Molecular Structure of Corn Oil



Mixed triglyceride, where R1, R2 and R3 represent key fatty acids including palmitic, oleic and linoleic acids.

The typical processing of corn oil includes refining, bleaching, and deodorizing steps which substantially remove free fatty acids, phospholipids, color, odor, and flavor components, as well as miscellaneous other non-oil components. The Food Chemicals Codex (FCC) has established

food grade specifications for corn oil in the U.S. food supply, including limits on fatty acids as well as physical and chemical properties of the oil.

The fatty acid composition of typical corn oil in the U.S. food supply (per 100 g oil and per 100 g fatty acids), the CODEX standards for key fatty acids (CODEX STAN 210-1999), FCC 11 specifications for the predominant fatty acids in corn oil (fatty acids present at >1%), and mean concentrations of the fatty acids in the corn oil that is the subject of this GRAS evaluation are summarized below (Table 1). As previously noted, the predominant fatty acids in food-grade corn oil include linoleic acid, oleic acid, and palmitic acid, followed by stearic and linolenic acids. Collectively, these five fatty acids typically account for more than 90% of corn oil by weight.

Table 1. Fatty Acid Composition of Typical Corn Oil

Nutrient	USDA[a] per 100 g oil (04518)	USDA[a] per 100 g fatty acid (04518)	CODEX per 100 g fatty acid	FCC 11 Specification (%)	GRAS Corn Oil [%; Mean, Range][b]
Total fat	100	-	-	-	-
Total fatty acids	95.201	100	-	-	-
C16:0 (palmitic acid)	10.579	11.108	8.6-16.5	8.0-19.0%	11.6 (11.3 - 12.0)
C18:0 (stearic acid)	1.848	1.94	ND-3.3	0.5-4.0%	2.2 (2.0 - 2.3)
C18:1(oleic acid)	27.333	28.7	20.0-42.2	19-50%	32.3 (30.8 - 33.1)
C18:2 (linoleic acid)	53.515	56.191	34.0-65.6	38-65%	51.5 (50.6 - 52.6)
C18:3(linolenic acid)	1.161	1.219	ND-2.0	≤2.0%	1.2 (1.1 - 1.3)

[a] USDA National Nutrient Database for Standard Reference, corn oil (04518); values for C18:1, C8:2, and C8: correspond to values reported for undifferentiated form. Total fatty acids represented by sum of saturated, monounsaturated, and polyunsaturated fatty acids

[b] Mean and range of three representative samples (see Table 6 for data from each sample; COAs provided in Appendix B)

Phytosterols

In addition to fatty acids, vegetable oils typically contain phytosterols, compounds that are structurally similar to cholesterol. The most abundant phytosterols in plants and the human diet are β-sitosterol, campesterol, and stigmasterol. Based on data from CODEX, levels of total sterols in crude vegetable oils commonly used in infant formula fat blends range from approximately 170 to 2,210 mg per 100 g oil (Table 2). Relative to other oils commonly used in infant formula, corn oil and low erucic acid rapeseed oil (i.e., canola oil) tend to contain the highest concentration of total sterols (upper range of 2,210 and 1,130 mg per100 g oil, respectively (Table 2). Similar to other oils, the predominant sterols in corn oil include β-sitosterol, campesterol, and stigmasterol, which account for a comparable proportion of total sterols relative to other oils commonly used in infant formula fat blends. Data from the USDA indicate that β-sitosterol, campesterol, and stigmasterol account for 621, 189, and 56 mg per 100 g oil, respectively, or approximately 866 mg phytosterols per 100 g oil (USDA 2018).

Table 2. Typical Total Sterols in Vegetable Oils and Percentages by Phytosterol

	Phytosterols per 100 g Crude Oil and Percent Contribution by Type (CODEX)[a]				
Phytosterol	Corn	Rapeseed (low erucic acid)	Safflower seed (high oleic acid)	Soy bean	Sunflower seed (high oleic acid)
Total sterols (mg/100 g)	700-2210	450-1130	200-410	180-450	170-520
Cholesterol, %	0.2-0.6	ND-1.3	ND-0.5	0.2-1.4	ND-0.5
Brassicasterol, %	ND-0.2	5.0-13.0	ND-2.2	ND-0.3	ND-0.3
Campesterol, %	16.0-24.1	24.7-38.6	8.9-19.9	15.8-24.2	5.0-13.0
Stigmasterol, %	4.3-8.0	0.2-1.0	2.9-8.9	14.9-19.1	4.5-13.0
Beta-sitosterol, %	54.8-66.6	45.1-57.9	40.1-66.9	47.0-60	42.0-70
Delta-5-avenasterol, %	1.5-8.2	2.5-6.6	0.2-8.9	1.5-3.7	1.5- 6.9
Delta-7-stigmastenol, %	0.2-4.2	ND-1.3	3.4-16.4	1.4-5.2	6.5-24.0
Delta-7-avenasterol, %	0.3-2.7	ND-0.8	ND-8.3	1.0-4.6	ND-9.0
Others, %	ND-2.4	ND-4.2	4.4-11.9	ND-1.8	3.5-9.5

[a] STANDARD FOR NAMED VEGETABLE OILS, CODEX STAN 210-1999; Adopted in 1999. Revised in 2001, 2003, 2009, 2017. Amended in 2005, 2011, 2013, 2015.
ND = not detected

Analytical data on the corn oil that is the subject of this GRAS evaluation as summarized in Table 3 demonstrate that the concentration of total phytosterols in corn oil is 777 mg per 100 g oil and the proportions of total plant sterols (by type) are comparable to proportions typically found in corn oil.

Table 3. Total Sterols and Percentages by Phytosterol in Corn Oil for Use in Infant Formula

	Batch			
Parameter	2017017	2023678	2028874	Average
Total sterols, mg/100g oil	800	750	780	777
Campesterol	20.6 %	20.3 %	20.4 %	20.4 %
Stigmasterol	6.7 %	7.3 %	6.9 %	7.0%
Beta-sitosterol	62.5 %	64.4 %	64.0 %	63.6%
Delta5-avenasterol	2.0 %	2.8 %	2.7 %	2.5%
Delta7-stigmasterol	0.3 %	0.1 %	0.2 %	0.2%
Delta7-avenasterol	1.5 %	1.2 %	1.2 %	1.3%
Campestanol	0.9 %	0.7 %	0.9 %	0.8%
Sitostanol	2.6 %	2.1 %	2.4 %	2.4%

Analytical data provided in Appendix B

Vitamins

Typical corn oil is a source of fat-soluble vitamins, including approximately 14.3 mg vitamin E (alpha-tocopherol) per 100 g oil and 1.9 µg vitamin K (phylloquinone) per 100 g oil (USDA,

2018). Vitamins E and K are not added during the manufacture of the oil, thus measured levels in the oil represent naturally occurring levels. Analytical data on the corn oil that is the subject of this GRAS evaluation as summarized in Table 4 demonstrate the vitamin E concentration of the oil is approximately 45 mg per 100 g oil and the concentration of vitamin K1 is in the range of 12.9 to 20.2 µg per 100 g oil. Concentrations of vitamin A and vitamin D are below limits of detection.

Table 4. Vitamins in Corn Oil for use in Infant Formula

Vitamin	Corn Oil Sample			Average
	1737780	1803331	1917272	
Vitamin E equivalent (d,α-tocopherol), mg/100 g	48	-	42.7	45.4-
Vitamin K1 (phylloquinone), µg /100 g	20.2	12.9	19.7	17.6
Vitamin A (retinol), µg /100 g	-	-	<21	-
Vitamin D, µg /100 g	-	-	<0.1	-

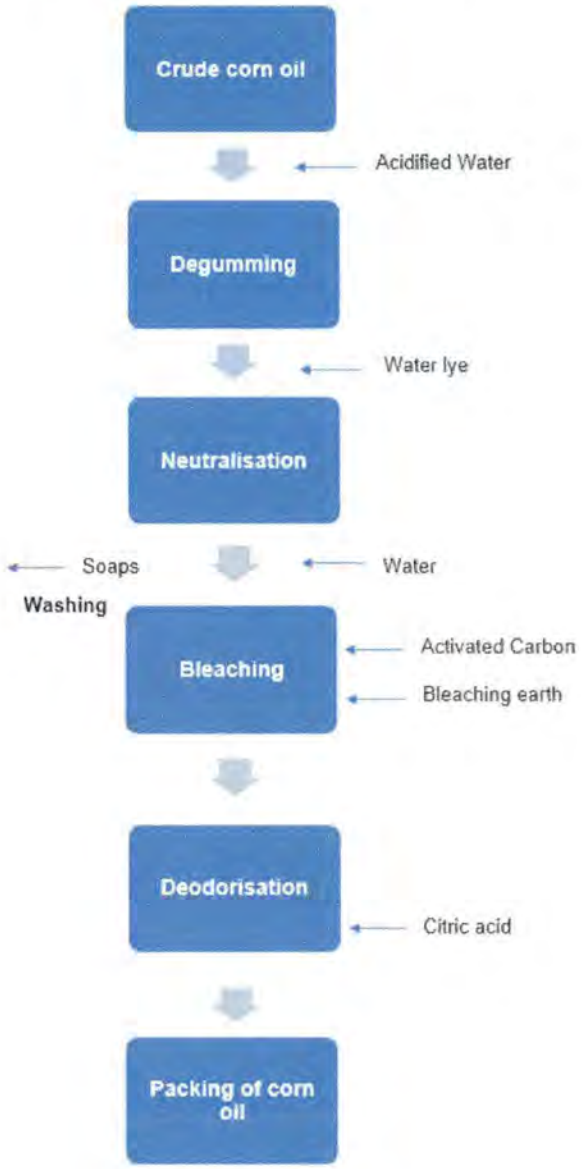
Method of Manufacture

The corn oil that is the subject of this GRAS review is extracted from the germ of the corn crop and subjected to refining, degumming, neutralization, bleaching, and deodorization in the manufacturing process to produce a safe, nutritious, edible oil with long shelf life, natural bright color, and neutral taste. The corn oil is manufactured in compliance with food safety and quality conditions consistent with current Good Manufacturing Practices (cGMP) as noted in Appendix A.

The production process is described below, and a flow diagram of the production process is provided in Figure 2. The refining process removes undesired components in the crude oil including free fatty acids, oxidation products, phospholipids, and waxes as well as known contaminants such as pesticides and polyaromatic hydrocarbons (PAHs). The degumming process removes lecithins, proteins, and other unsuitable compounds from the oil. This process step involves mixing the crude oil with acidified water which allows the water-soluble phospholipids to be removed. Neutralization removes free fatty acids and proteins by the addition of water lye, transforming the free fatty acids into a soap, which is then washed out along with other impurities such as proteins. Bleaching of the neutralized oil removes color pigments, metals, and oxidation products. The neutralized oil is treated with bleaching earth under vacuum which absorbs the impurities over a set time. The particles are then filtered out, resulting in a lighter oil. In some cases, activated carbon is also used as a processing aid to remove heavy PAHs. The bleaching earth and activated carbon are removed by filters. Deodorization is the final step of the refining process, which ensures the removal of any possible volatile substances (i.e., taste and odor compounds) as well as contaminants (i.e., pesticide residues and light PAHs). Deodorization is a steam distillation process which is attained by ensuring a high steam temperature in a vacuum over a set time, thus removing volatile substances while retaining vitamins and sterols. Citric acid is added during deodorization as a

chelating agent. After deodorization, the corn oil passes through a final filter before the fully refined oil is released for distribution.

Figure 2. Flow Diagram of the Production Process of Corn Oil



Specifications

As shown in Table 5, the corn oil that is the subject of this GRAS determination meets specifications consistent with FCC 11 specifications for color, linolenic acid (C18:3) and other key fatty acids levels, peroxide value, iodine value, free fatty acids level, moisture, arsenic, lead, and unsaponifible matter.

Table 5. Specifications and Methods of Analysis for Corn Oil for use in Infant Formula

Parameter	FCC 11	Specification		Method
		Lower Limit	Upper Limit	
Color 5 1/4" yellow	-	-	20.0	Lovibond Tintometer
Color 5 1/4" red	NMT 5.0	-	2.0	
C16:0, %	8.0-19.0	9	13.0	IUPAC 2.304
C18:0, %	0.5-4.0	1	3.0	
C18:1, %	19-50	24	42.0	
C18:2, %	38-65	49	62.0	
C18:3, %	NMT 2.0	-	2.0	
Peroxide value, mEq/kg	NMT 10	-	0.5	AOCS Cd 8b-90(m)
Flavor	-	-	-	Sensoric
Iodine	120-130	118	128	IUPAC 2.205(m)
Free fatty acids, %	NMT 0.1	-	0.10	IUPAC 2.201(m)
Water	NMT 0.1	-	0.1	AOCS Ca 2e-84
Arsenic, mg/kg	NMT 0.5	-	0.1	
Lead, mg/kg	NMT 0.1	-	0.01	
Unsaponifiable matter, %	NMT 1.5	-	1.5	DIN EN ISO 3596
NMT – not more than				

Data from representative non-consecutive batches of corn oil presented in Table 6 data demonstrate that the oil meets these specifications. Data in Table 7 demonstrate that the corn oil meets FCC specifications for lead and arsenic and data in Table 8 demonstrate that the corn oil meets FCC specifications for unsaponifiable matter. Additionally, analytical data from representative batches of the corn oil show that concentrations of all fatty acids in the corn oil are consistent with ranges as specified in FCC 11 (see Appendix B).

Table 6. Batch Data for Key Parameters in Corn Oil for use in Infant Formula

Parameter	Specification		Batch Data			
	Lower Limit	Upper Limit	1981011 (2018-09-25)	1956365 (2018-07-16)	1926400 (2018-05-02)	1941815 (2018-06-13)
Color 5 1/4" yellow	-	20	6.2	6.8	6.0	4.7
Color 5 1/4" red	-	2	0.9	1	0.8	0.5
C16:0, %	8	13	11.6	12	11.3	11.6
C18:0, %	1	4	2.3	2.3	2	2.1
C18:1, %	24	42	33.1	30.8	32.5	32.8
C18:2, %	52	62	50.6	52.6	51.7	51.2
C18:3, %	-	2.2	1.1	1.2	1.3	1.1
Peroxide value, mEq/kg	-	1	<0.1	<0.1	0.1	<0.1
Flavor	-	-	Approved	Approved	Approved	Approved
Iodine	118	128	121	122	122	122
Free fatty acids, %	-	0.1	0.02	0.02	0.04	<0.01
Water	-	0.1	0.02	0.02	0.02	-
Certificates of Analysis provided in Appendix B						

Table 7. Specifications and Batch Data for Arsenic and Lead in Corn Oil for use in Infant Formula

Characteristic	Specification		Batch Data		
	Lower Limit	Upper Limit	Sept 2015	Oct 2017	Jan 2018
Arsenic, mg/kg	-	0.1	<0.02	<0.02	<0.02
Lead, mg/kg	-	0.01	<0.01	<0.01	<0.01

Table 8. Specifications and Batch Data for Unsaponifiable Matter in Corn Oil for use in Infant Formula

Characteristic	Specification		Batch Data		
	Lower Limit	Upper Limit	2017017	2023678	2028874
Unsaponifiable matter, %	-	1.5	1.0	1.0	1.1

Analytical data provided in Appendix B

In addition to the parameters assessed as part of the product specifications in Tables 5, 6, and 7, ingredient specifications are in place to ensure that the corn oil meets established limits for potential contaminants of concern, including other metals (i.e., cadmium, mercury), microorganisms (i.e., general and pathogenic, including *Salmonella* and *Enterobacteriaceae*), mycotoxins, dioxins and dioxin-like PCBs, non-dioxin-like PCBs, glycidyl fatty acid esters, , polycyclic aromatic hydrocarbons (PAHs), pesticides, radioactivity, and solvents. The reference limits for potential contaminants of concern in corn oil are limits established in EU regulations for ingredients in infant foods, Codex standards, and internal standards.

The specifications for other metals, mycotoxins, and microbiological parameters are shown in Table 9 along with analytical data from a representative sample; Table 10 presents specifications for dioxins and dioxin-like PCBs, non-dioxin-like PCBs, glycidyl fatty acid esters, polycyclic aromatic hydrocarbons (PAHs), pesticides, radioactivity, and solvents. Analytical data on corn oil, representative specifications for contaminants in oils sourced for use in infant formula, and assurances that specifications for compliance are met for corn oil are presented in Appendix C.

Table 9. Specifications and Representative Data for Cadmium, Mercury and Mycotoxins in Corn Oil for Use in Infant Formula

Component	Maximum Residue Limit	Unit	Representative Sample No 171104892
Cadmium	0.005	mg/kg	<0.005 mg/kg
Mercury	0.01	mg/kg	<0.01 mg/kg

Component	Maximum Residue Limit	Unit	Representative Sample No 171104892
Aflatoxin B1	0.10	mcg/kg	<0.01 mcg/kg
Aflatoxin B2	-	-	<0.01 mcg/kg
Aflatoxin G1	-	-	<0.01 mcg/kg
Aflatoxin G2	-	-	<0.01 mcg/kg
Sum Aflatoxins B/G	-	-	<0.01 mcg/kg
Ochratoxin	0.50	mcg/kg	<0.5 mcg/kg
Deoxynivalenol (DON)	200	mcg/kg	<50 mcg/kg
Zearalenone	20	mcg/kg	<10 mcg/kg
Fumonisins (B1 + B2)	200	mcg/kg	
Total plate count	100	CFU/g	<100
Yeast	10	CFU/g	<10
Mold	10	CFU/g	<10
Enterobacteriaceae	Absent	/10 g	Negative
Cronobakter sakazaki	Absent	/10 g	Negative
E coli	Absent	/1 g	Negative
Listeria monocytogenes	Absent	/25 g	Negative
Salmonella	Absent	/25 g	Negative

Table 10. Specifications for Cadmium, Mercury and Mycotoxins in Corn Oil for Use in Infant Formula

Component	Maximum Residue Limit	Unit
Sum of dioxins (WHO-PCDD/F-TEQ)	0.3	pg/g fat
Sum of dioxins and dioxin-like PCB's (WHO-PCDD/F-PCB-TEQ)	0.5	pg/g fat
Sum of PCB28, PCB52, PCB101, PCB138, PCB153, PCB18	1.0	ng/g fat
Glycidyl fatty acid esters expressed as glycidol	300	mcg/kg
Bens(a)pyrene (BaP)	1.0	mcg/kg
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	2.0	mcg/kg
Acetone	1	mg/kg
Hexane	1	mg/kg
Methanol	10	mg/kg

Technical Effect

Lipids are the predominant source of energy for infants, accounting for approximately 45-55% of total energy intake in human milk and formula (Koletzko et al. 2005). Infant formulas are produced using a combination of fat sources, predominantly vegetable oils, designed to mimic the fatty acid profile and absorption of human milk (Heird 2007). The intended technical effect of corn oil in calorically-dense, ready-to-feed exempt infant formula is to contribute fatty acids primarily in the form of linoleic acid, oleic acid, and palmitic acid to the fat blend.

Part 3. Dietary Exposure

Proposed Use and Level

The intended use of corn oil is to provide a source of fat. The proposed maximum use of corn oil in exempt infant formula for term infants with calorically dense formula needs and/or requiring a fluid restriction is 3.0% of the fat blend by weight. 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 contribution of fat to total energy intake of human milk or formula is approximately 48 to 50% (IOM, 2005; Martin et al., 2016). The daily intake of corn oil from the proposed use in calorically dense formula was estimated assuming (1) the fat blend accounts for 50% of total energy in the formula, which provides a conservatively high estimate of energy as fat, (2) a maximum concentration of 3.0% corn oil in the fat blend by weight, and (3) formula intake representative of intakes among the population of term infants requiring a calorically dense infant formula or with fluid restrictions.

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 corn oil from the proposed use in calorically dense infant formula.

As summarized in Table 9, 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 11. 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	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	age: 76 (30-182) days bw: 3.94 (3.29-5.80) kg	2 x calculated resting energy requirement (based on	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
	n = 76; 30 (21-54) days on formula (median, interquartile range)	(median, interquartile range)	Schofield equation for weight)	
INGROTO, 2012 (un-published)	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

The mean level of intake of the calorically dense infant formula achieved across most studies was up to approximately 120 kcal/kg bw/day, which therefore represents a reasonable estimate of typical formula 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 1 kcal/mL; therefore, 120 kcal/kg bw/day is equivalent to 120 mL/kg bw/day of formula.

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 1 kcal/ mL, intake of 175 kcal/kg bw/day is equivalent to 175 mL/kg bw/day of formula. Typical formula intake can be assumed to be 120 kcal/kg bw/day, which is the upper end of the range intake reported in all other studies.

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.

Corn Oil Intake

Assuming the fat blend accounts for 50% of total energy in the formula and corn oil is a maximum of 3.0% in the fat blend by weight, estimated intake of corn oil is 0.20 g/kg bw/day for

an infant consuming formula at a typical rate of 120 mL/kg bw/day, and 0.29 g/kg bw/day for an infant consuming formula at a high rate of 175 mL/kg bw/day (Table 10).

The calorically dense infant formula is intended for infants weighing up to 9 kg. Assuming this maximum body weight, consumption of formula at the typical rate of 120 mL/kg bw/day will deliver 1.8 g corn oil and consumption of formula at the high rate of 175 mL/kg bw/day will deliver 2.6 g corn oil. For infants weighing in the range of 4-5 kg (e.g., 4.5 kg), intake of corn oil is estimated at 0.9 or 1.3 g for a typical or high consumer of the infant formula, respectively.

Phytosterol Intake

Corn oil is a source of phytosterols, with each 100 g of oil typically providing 777 mg total phytosterols based on analytical data as shown in Table 3. Assuming the maximum intended use of 3.0% corn oil in the fat blend in a formula with 50% of calories from fat and a typical phytosterol concentration of 777 mg per 100 g corn oil, the corn oil fraction will contribute 1.3 mg phytosterols per 100 kcal formula. Infant formula consumed at a typical formula intake of 120 kcal/kg bw/day therefore provides an estimated 1.6 mg phytosterols per kg bw/day, and formula intake at a level of 175 mL/kg bw/day, which represents a high intake, provides an estimated 2.3 mg phytosterols per kg bw/day (Table 10).

Table 12. Estimated Daily Intake of Corn Oil and Phytosterols from the Maximum Proposed Use of Corn Oil

Calorically Dense Formula Intake		**Total fat Intake** [b]	**Corn Oil Intake**	**Phytosterol Intake from Corn Oil**[d]
Level of intake	**kcal/kg bw/day**	**g/kg bw/day)**	**g/kg bw/day**	**mg/kg bw/day**
Typical [a]	120	6.7	0.20	1.6
High	175	9.7	0.29	2.3

[a] 100 kcal per 100 mL
[b] Assume fat accounts for 50% of kcal, and 9 kcal per gram of fat
[c] Assume maximum use of 3.0% corn oil in fat blend
[d] Assumed average total phytosterol concentration of 777 mg per 100 g oil (see Table 3)

For infants weighing approximately 4.5 to 9.0 kg, consumption of formula at the typical rate of 120 mL/kg bw/day will deliver 7 to 14 mg phytosterols, and consumption of formula at the high rate of 175 mL/kg bw/day will deliver 10 to 20 mg phytosterols.

Part 4. Self-Limiting Levels of Use

Corn oil is intended for use as a component of the fat blend in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction at a concentration not to exceed 3.0% of the fat blend by weight. 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 corn oil as a component of the fat blend in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is based upon scientific procedures.

Part 6. Narrative

Nutritional Role of Fats in Infant Formula

Lipids are the predominant source of energy for infants, accounting for approximately 45-55% of total energy intake in human milk and formula (Delphanque et al. 2015). These lipids are present predominately (>95%) in the form of triglycerides (three fatty acids esterifed to a glycerol backbone). Infant formulas typically contain a blend of vegetable oils, although additional fat sources may also include fats such as dairy fat, single cell oils, fish oils, egg phospholipids, and structured lipids. The specific blend of vegetable oils, and potentially other fat sources, is designed to mimic the fatty acid profile and absorption of human milk.

Fat and Essential Fatty Acid Requirements of Infant Formula

Nutrient requirements for infant formula in the United States include limits on the level of protein, fat, and the essential fatty acid linoleic acid, and concentrations of micronutrients (21 CFR §107.100) (Table 11). The regulations specify that infant formula provide between 3.3 and 6.0 g total fat per 100 kcal and that fat accounts for 30 to 54% of the energy in formula. Additionally, infant formula must contain a minimum of 300 mg linoleic acid per 100 kcal and a minimum of 2.7% of calories. These limits are also applicable to exempt infant formulas unless the infant formula is not generally available at the retail level (i.e., accessible through medical prescription for dietary management of specific diseases) and the formulation meets the necessary quality factors (21 CFR §107.50). Infant formula nutrient requirements do not specify limits on other fatty acids or phytosterols, nor do the requirements specify which fat sources may or may not be used. Previously low erucic acid rapeseed oil and partially hydrogenated low erucic acid rapeseed oil (i.e., canola oils) were prohibited from use in infant formula (21 CFR §184.1555), although use of low erucic acid rapeseed oil was concluded to be GRAS for use as a source of fat in term infant formulas at levels up to 31% of total fat blend in 2012 (GRN 425); FDA responded to this notification with a letter of no questions (FDA 2012).

Since establishment of most nutrient requirements in infant formula in the U.S. as detailed by FDA (21 CFR §107.100), the Life Sciences Research Office (LSRO) Expert Panel (1998) reviewed the available evidence and recommended that infant formulas for term infants provide 4.4 to 6.4 g fat per 100 kcal, 8 to 35% of total fatty acids as linoleic acid, 1.75 to 4.0% fat as α-linolenic acid, and a ratio of linoleic acid to α-linolenic acid of at least 6:1 and not more than 16:1. The recommendation to include specifications for α-linolenic acid resulted from evidence indicating that α-linolenic acid is a precursor for the formation of n-3 long chain polyunsaturated fatty acids, including docosahexaenoic acid (DHA) (Table 11). Codex and European Commission standards for infant formula include similar though not identical specifications for total fat and essential fatty acids (Table 11). The Codex specifications for infant formula prohibit the use of hydrogenated fats and oils and EC standards prohibit the use of cottonseed oil and sesame seed oil, though these international regulations and the FDA do not provide further guidance on the suitability of specific fats and oils for use in infant formula that would prohibit use of corn oil in infant formula.

Table 13. Fat and Fatty Acid Requirements in Infant Formula for Term Infants

Reference	Limits on Total Fat per 100 kcal	Limits on Linoleic Acid (LA)	Limits on α-Linolenic Acid (ALA)	Limits on ratio of LA:ALA
21 CFR §107.100 Regulation for US, term infant formula	3.3-6.0 g (30-54% of calories)	minimum of 300 mg/100 kcal (minimum of 2.7% of calories)	-	-
LSRO 1998 Recommendations from LSRO for FDA, term infant formula	4.4-6.4 g	8-35% of total fatty acids (350-2240 mg/100 kcal)	1.75-4% of total fatty acids (77-256 mg/100 kcal)	6:1 to 16:1
Codex Stan 72-1981, rev 2007 International standard for standard formula and formula for special medical purposes [a]	4.4-6.0 g	minimum of 300 mg/100 kcal; guidance upper level of 1400 mg/100 kcal	minimum of 50 mg/100 kcal; maximum not specified	5:1 to 15:1
Current: Directive 2006/141/EC [b] EC for standard formula; also for special medical purposes [c]	4.4-6.0 g	300-1200 mg/100 kcal	≥ 50 mg/100 kcal	5:1 to 15:1
Forthcoming: Commission Delegated Regulation (EU) 2016/127; Regulation (EU) No 609/2013 [d] EC Standard and for special medical purposes	4.4-6.0 g	500-1200 mg/100 kcal	50-100 mg/100 kcal	-

[a] Unless modified to meet special nutritional requirements arising from the disease(s), disorder(s) or medical condition(s) for whose dietary management the product is specifically formulated, labelled and presented.
[b] In effect to 21 February 2020; then repealed by Delegated Regulation (EU) 2016/127.
[c] Unless modified to meet special medically-determined nutritional requirements.
[d] In effect from 22 February 2020 (replaces Directive 2006/141/EC).

Oils Commonly Used in Infant Formula and their Fatty Acid Profiles

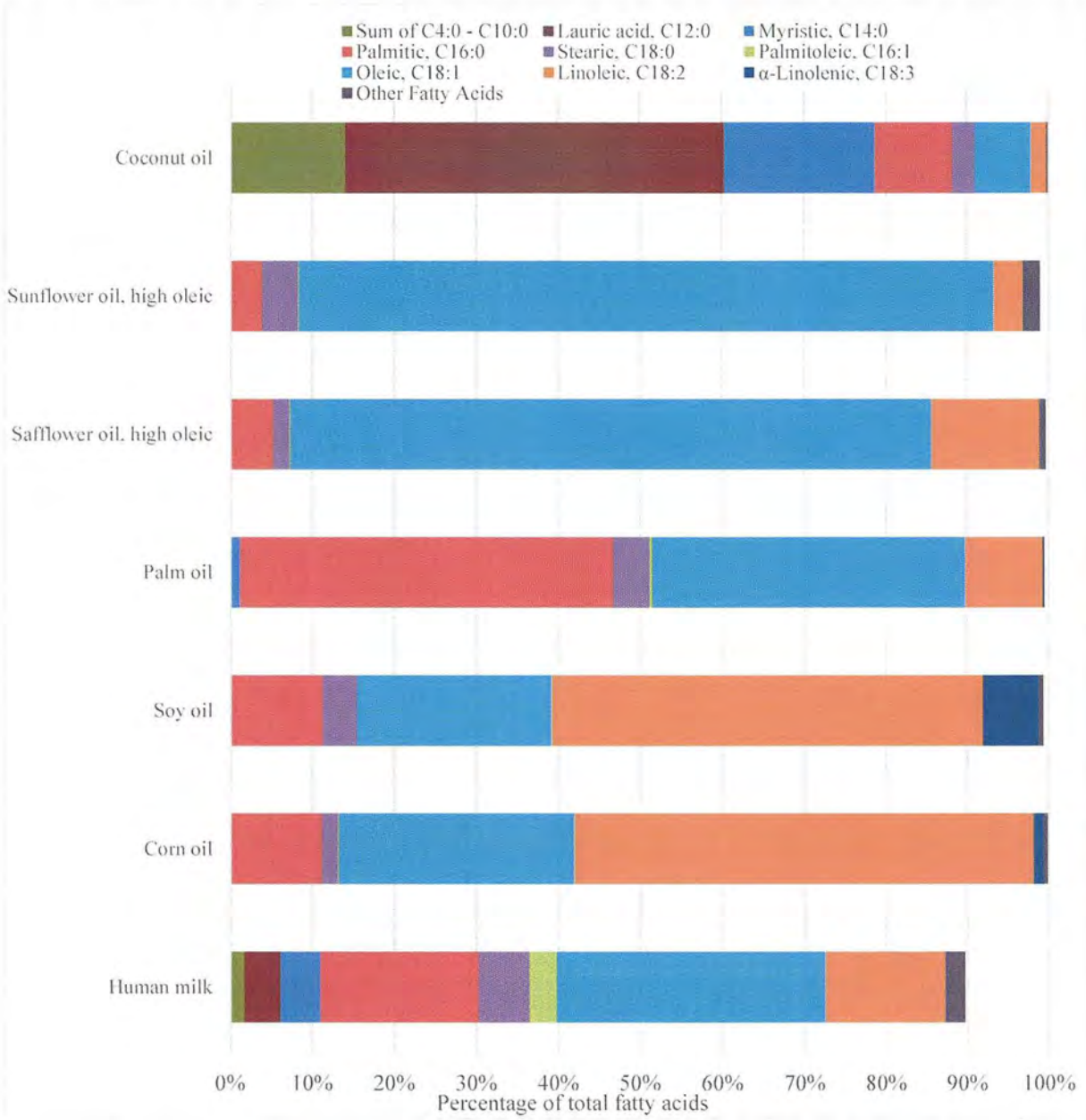
As previously noted, infant formulas typically contain a blend of vegetable oils, potentially in combination with other oils and fats such as dairy fat to achieve a desired fatty acid profile that typically mimics the key fatty acids in human milk. Commonly used vegetable oils in infant formula currently available in the U.S. include soy, high oleic safflower, high oleic sunflower, palm olein, palm, and coconut.

Corn oil is a food with a long history of use in the U.S. food supply (Corn Refiners Association, 2006). While not as widely used as some vegetable oils, corn oil is indeed used in infant formulas globally and in select products available in the U.S. marketplace. The available literature also indicates that corn oil was commonly used in infant formulas in the U.S. as

recently as the late 1990s. The LSRO Expert Report (1998), for example, lists corn oil, along with soy and high-oleic safflower and sunflower oils, as the most commonly used sources for unsaturated fatty acids in infant formula and is used in combination with coconut or palm oil. The LSRO Expert Report notes that infant formulas with corn oil have a particularly high concentration of fatty acids as linoleic acid (in excess of 35%), though noted that the formulas were used without noted adverse effects. Corn oil was traditionally used rather than soy oil in powdered formulas as the lower concentration of α-linolenic acid in corn oil was less susceptible to oxidative degradation (Ponder et al., 1992). The recent published literature also includes references to use of corn oil in extensively hydrolyzed and reduced mineral infant formulas produced in the U.S. (summarized by Green Corkins and Shurley, 2016).

The concentration of key fatty acids in corn oil, vegetable oils commonly used in infant formula, and human milk are summarized in Figure 3. The fatty acid profile of human milk is distinct from the profile in any of the vegetable oil commonly used in infant formula, thus supporting the practice of blending various oils to achieve the desired profile. The primary fatty acids shown in Figure 3 are present in all of the vegetable oils, though the percentage of total fatty acids varies. Corn oil is a rich source of linoleic acid, which contributes to the target ratio of linoleic to α-linolenic acid. Relative to high oleic sunflower and safflower oils, corn oil provides a lower proportion of fatty acids as oleic acid and a higher proportion as palmitic acid. In general, among the oils commonly used in infant formula, the fatty acid profile of corn oil is most similar to soy oil.

Figure 3. Typical Fatty Acid Profile in Human Milk and Oils Used in Infant Formula Fat Blends



Sum of C4:0 - C10:0 for human milk does not include C4:0, C6:0 fatty acids.
Palmitoleic acid content is the sum of undifferentiated C16:1; Oleic acid content is the sum of undifferentiated C18:1; Linoleic acid content is the sum of undifferentiated C18:2. Alpha-linolenic acid content unavailable for palm and sunflower oil; value assumed to be sum of undifferentiated 18:3 for these oils.
Sources: USDA National Nutrient Database for Standard Reference for Corn (04518), Soybean (04669), Palm (04055), Safflower (04511), Sunflower (04584), and Coconut (04047) Oil; Human milk: Yuhas et al., 2006

Digestion and Absorption of Fat by the Infant

Lipids are the predominant source of energy for infants, accounting for approximately 45-55% of total energy intake in human milk and formula (Delphanque et al., 2015), and these lipids are present predominately (>95%) in the form of triglycerides. Triglycerides contain a glycerol backbone to which three fatty acids are esterified. The location of the fatty acid on the glycerol backbone is referred to by stereospecific numbering, with the end positions identified as sn-1 and sn-3 (the α positions), and the middle position identified as sn-2 (the β position).

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. Corn oil contributes fatty acids primarily in the form of linoleic acid, oleic acid, and palmitic acid. A healthy full-term infant has a functional digestive system at birth, though digestive enzymes may be present at a lower level compared to levels in older infants (reviewed in Zou et al., 2016). Term infants consuming the calorically dense formula with corn oil would reasonably digest and metabolize triglycerides, as do other term infants consuming breast milk or standard infant formula.

Digestion of triglycerides in infants begins with the secretion of gastric lipase from gastric mucosal cells. The lipase hydrolyzes fatty acids from the sn-3 position of the triglyceride, leaving sn-1,2 diacylglycerols (Innis, 2011). Pancreatic colipase-dependent lipase released from the pancreatic acinar cells then hydrolyzes the sn-1,3 ester linkages, resulting in a sn-2 monoacylglycerol and unesterified fatty acids products (Innis 2011). Additional lipases released from the pancreas (carboxyl ester lipase and pancreatic lipase related protein 2), lipase secreted from the mammary gland (milk bile salt-stimulated lipase), and salivary lipases may also contribute to digestion of lipids (Innis 2011; Zou et al., 2016). The triglyceride digestion products cross the apical membranes of the enterocytes and are reassembled into triglycerides, packaged into chylomicrons, and secreted into circulation (Innis, 2011).

In human milk, approximately 98% of the fat is present in form of triglycerides (Innis, 2011), with saturated and unsaturated fatty acids esterified to a glycerol backbone. Triglycerides in human milk and infant formula differ in the distribution of long-chain saturated fatty acids. The predominant saturated fatty acid in human milk is palmitic acid (16:0) and approximately 70% or more of the palmitic acid is esterified in the sn-2 position or beta-position whereas 50-70% of fatty acids in the sn-2 position are linoleic acid (18:2) in corn and soybean oils (Innis 2011). In vegetable oils, 5-20% of the palmitic acid is esterified in the sn-2 position, while in milkfat approximately 40% of palmitic acid is in the sn-2 position (Berger et al., 2000).

Clinical Studies of Infants Consuming Corn Oil

Corn oil has been used as a component of the fat blend in infant formulas and results from clinical trials using such products provide evidence to support the suitability of this oil in the fat blend. A search of the published literature for additional clinical studies in which corn oil intake was provided as a component of infant formula was conducted via PubMed using the search terms (infant OR newborn OR formula) AND ("corn oil" OR "maize oil") with limits for human studies and papers in the English language. The search was lasted updated March 3, 2019

(yielding a total of 87 citations). Titles and abstracts were screened for interventions containing corn oil and several studies were identified.

Infant Formula Containing Corn Oil

The published research literature provides evidence that corn oil was commonly used in commercial infant formulas as recently as the 1990s. Given the routine use of corn oil in the fat blend, infant formulas containing corn oil were commonly used as control formulas for comparison in clinical trials. For example, Lloyd and colleagues (1999) reference use of a widely used commercial product (Similac with Iron powder) which had a fat blend consisting of 50% corn oil, 38% coconut oil, and 12% soy oil during the 2-week baseline period prior to randomization to a test product.

Results from some of the intervention studies in which commercially available infant formulas containing corn oil as a component of the fat blend were provided to infants provide evidence that the fat blend supported growth without adverse events. Infant formula with corn oil accounting for 50% of the fat blend was demonstrated to support normal growth over a period of 8 weeks in a study of healthy term infants compared to formula containing 60% soy oil in the fat blend or human milk (Ponder et al., 1992). There was no difference in percentages of DHA in plasma or red blood cells with consumption of the corn oil formula compared to the soy oil formula, but the percentages were lower compared to infant fed human milk (Ponder et al., 1992). Commercial infant formula based on corn oil (accounting for an unspecified percent of fat blend) designed for preterm infants also demonstrated normal growth compared to formula based on soy oil in an intervention of infants from 30 to 57 weeks postconceptional age (Uauy et al., 1990; Uauy et al., 1994; Hoffman et al. 1999). Additional published and unpublished studies designed to examine the effect of infant formula on an aspect of efficacy or a metabolic parameter provide further evidence that fat blends containing corn oil support growth and lipid responses that are consistent with expected responses (De Souza et al., 2018; Golawin and Pomeranze, 1962; Hayes et al., 1992; Leite et al., 2013; Schouten 2013). Studies monitoring consumption of corn oil in complementary foods provide corroborative evidence of the safety of intake of corn oil as a component of dietary fat in infants and very young children (Libuda et al., 2016; Schwartz et al., 2009). Details of the identified studies are provided below.

Ponder and colleagues examined levels of DHA in plasma and red blood cells among term infants fed a powdered or liquid infant formula or human milk for 8 weeks in a randomized, parallel study in hospitals in the U.S. (Ponder et al., 1992). The powdered commercial formula (Similac with Iron 20 powder, Ross Laboratories, Columbus, OH) contained 50% corn oil and 50% coconut oil (by volume) and the commercial liquid formula (Similac with Iron 20 ready-to-feed) contained 60% soy oil and 40% coconut oil (by volume). The fatty acid composition of the formula fats differed primarily in the percentage of α-linolenic acid (ALA) and the ratio of linoleic acid (LA) to α-linolenic acid, with an ALA content of the corn and soy formulas of 0.8 and 4.5 g per 100 g of total fatty acids (0.4 and 2.3% total energy), respectively, and a LA to ALA ratio in the soy formula of 7:1 and a ratio of 39:1 in the corn formula. Infants were enrolled at birth, assigned to the feeding group, and followed for 8 weeks during which they were fed exclusively the designated formula or breast milk. A total of 43 infants completed the study: 18 in the human milk group, 11 in the soy oil group, and 14 in the corn oil group. Intake of the corn and soy oil formulas was similar, with the mean intake over the study ranging

between 101 and 125 kcal/kg bw/day in both formula groups. Growth did not differ among groups. There were no statistically significant differences in the percentages of DHA in the plasma or red blood cell (RBC) phosphatidylcholine and phosphatidylethanolamine between infants fed formula from soy oil and infants fed formula from corn oil. Infants fed formula had significantly lower plasma and RBC DHA levels than infants fed human milk.

The safety of infant formula based on soy oil supplemented with marine oils was compared to a control formula based on corn oil in a clinical trial of infants in preterm infants with very low birth weight from 30 weeks postconceptional age through 57 weeks postconceptional age (Uauy et al., 1990; Uauy et al., 1994; Hoffman et al. 1999). Eighty-three infants with low birth weight (1.0-1.5 kg) were breast-fed or assigned to consume one of three formulas designed to have varying fatty acid compositions. The fat sources in the three formulas were provided by unspecified proportions of corn oil with medium chain triglycerides and coconut oil (a commercial powdered formula for premature infants (existing before 1987; Enfamil Premature, Mead-Johnson Bristol-Myers Co, Evansville, IN); soy oil with medium chain triglycerides and coconut oil test formula; or soy oil with medium chain triglycerides and coconut oil, marine oil, and corn oil test formula. Anthropometrics, formula tolerance, retinal function, coagulation, RBC membrane fluidity, and plasma vitamin A and E levels were monitored during weeks 36 and 57 of postconceptional age. Of the 83 infants that entered the trial, data were available from 70 infants at 40 weeks postconceptional age and from 52 infants at the 57-week postconceptional age follow-up. Medical complications throughout the trial included respirator treatment, congenital infection or malformation, gastrointestinal surgery, hemorrhage, retinopathy (n=1), or blood transfusions (n=5). Mortality rates were similar across all groups. Absolute measurements and z-scores of weight, length, and head circumference were not significantly different between treatment groups and the breastfed control group throughout the intervention or at follow-up. The number of days to reach 1.8 kg body weight was significantly longer among breast fed infants, but there was no difference in duration among the formula treatment groups and energy intakes among the formula feed and breast milk feed infants were not significantly different. Bleeding time, plasma vitamin A, and vitamin E were within normal ranges for all groups and RBC membrane fluidity was not affected by the intervention.

In the more recent literature, studies in which a commercial formula containing corn oil in the fat blend also were identified. De Souza and colleagues (2018) and Leite and colleagues (2013) investigated the effects of formula lipid profile on absorption of fat, fatty acid acids, and calcium balance among healthy infants. This study was conducted with commercially available formulas in Brazil. One formula was a powder containing a fat blend comprised of 10.9% corn oil, 44% palm olein oil, 21.7% palm kernel oil, 18.5% canola oil, 2.8% milk fat, and 2.1% of a mixture of DHA, ARA, and soy lecithin. The other powder formula contained a fat blend comprised of 41.4% high oleic sunflower oil, 29.6% coconut oil, and 27.6% soy oil, and 1.4% of a mixture of DHA and ARA. Each formula was consumed for 14 days in the sample of 33 infants ages 68 to 159 ± 3 days at enrollment followed by a 4-day metabolic testing period in 17 male participants. Formula intake and adverse event incidence was not significantly different between formula treatment groups. During the 4-day metabolic period, stool frequency was significantly higher and mean stool consistency score was significantly lower (indicating an increased percentage of formed stools) with consumption of the corn oil containing formula though differences between the groups were not significant during the tolerance period (Leite et al. 2013). Fecal fat excretion was significantly higher and calcium absorption was significantly lower among infants

consuming the formula containing predominantly palm olein oil with corn oil, and the investigators suggested that the high fecal fat excretion was likely attributed to the high palm olein oil content of the formula.

Calorically dense infant formula containing corn oil has been the test article in an unpublished, multi-center, single arm trial (Schouten 2013). Fifty healthy term infants in Thailand and Indonesia (delivered 37-42 weeks gestation) consumed a cow's milk based infant formula providing 1.0 kcal/mL for a period of 6 weeks. The modified fat blend in the formula contained 11.5% corn oil by weight and 49% milk fat. Throughout the study, investigators monitored gastrointestinal tolerance, anthropometrics, and adverse events associated with the formula treatment. The investigators reported a low number of adverse events possibly attributed to the formula. Based on data from a historical control group of Asian infants, no difference in the severity and occurrence of gastrointestinal symptoms was observed. Results from this study provide supportive evidence of the suitability of corn oil as a component in the fat blend of infant formula.

Earlier studies with corn oil as a component of the fat blend in the infant diet provide evidence that the infant lipoprotein response to dietary fat is generally consistent with expected responses.

Among the identified studies was a trial examining the effects of corn oil compared with evaporated milk (a common source of infant feeding more than 50 years ago) on blood cholesterol levels (Golawin and Pomeranze, 1962). Infants consuming infant formula containing corn oil daily for 12 weeks had lower serum cholesterol levels than either infants fed evaporated milk or breast-fed infants. Serum cholesterol levels among corn oil fed infants rose to levels comparable to those of infants who consumed evaporated milk group following introduction of complementary foods at 16 weeks.

An earlier trial investigated the effect of varied fatty acid content and profile of two fat-modified milk formulas versus breast milk on body weight gain and blood lipids (Hayes et al., 1992). Forty-five healthy infants were randomly assigned to be breastfed, consume a corn oil and soybean oil formula, or a coconut oil and soybean oil formula for four months. The corn oil-containing formula was designed to be a low-fat, high polyunsaturated formula and provided 35% of energy as fat, with each 100 kcal providing 3.1 g corn oil and 0.8 g soy oil, thus corn oil accounted for 75% of the fat blend by weight. The comparator formula was similar in total, polyunsaturated, and saturated fat content as human breast milk and provided 50% of energy as fat, with 3.0 g coconut oil and 2.4 g soy oil per 100 kcal. Infants on both formulas had similar formula intake, exhibited similar weight gain as the breastfed infants, and without adverse events at 4 months. Infants in the corn and soy oil formula group consumed on average 535 kcal per day, or approximately 16.6 g of corn oil. Plasma total cholesterol, total lipids, triglycerides, ApoB and ApoB/ApoA-1 were significantly lower in infants fed the corn and soy oil formula compared to the infants fed human milk and the coconut and soy oil formula after 3 months of formula consumption. In addition, levels of low density lipoprotein cholesterol and low density lipoprotein/high density lipoprotein (LDL/HDL) cholesterol levels were significantly lower among infants fed the corn and soy oil formula compared to breastfed infants. Consumption of formula with corn and soy oil also led to a significantly different plasma and red blood cell fatty acid profiles compared to the breast-fed infants. The observed infant lipid responses were therefore generally consistent with responses observed in adults and reflective of the fat concentration and fatty acid profile of the formula or milk consumed.

Complementary Foods Containing Corn Oil

The effects of corn oil incorporated into complementary foods have also been evaluated in two clinical trials. In a double-blind, randomized controlled trial infants consumed commercially available complementary foods with corn oil (3.4 g) or rapeseed oil from 4 to 10 months of age (Schwartz et al., 2009). Feed intake and body weight gain were not significantly different between the two treatment groups, and a similar number of children refused the treatment complementary foods in each group. The percent of total plasma fatty acids that were n-3 and EPA and DHA levels were significantly lower with consumption of the corn-oil complementary foods compared the foods with rapeseed oil.

In another randomized controlled trial, infants between the ages of 4 to 10 months were provided with complementary foods containing corn oil (control group), rapeseed oil, or oily fish (Libuda et al., 2016). The control products providing corn oil or the intervention products providing rapeseed oil were reported to differ only in the oil source; products containing rapeseed oil contained on average 1.4 g of rapeseed oil per 100 g food. Body weight gain was similar with consumption of all complementary foods. There were no treatment related adverse events associated with consumption of the corn oil complementary foods. Erythrocyte and plasma DHA and EPA levels were significantly higher and LA levels significantly lower with consumption of the fatty fish complementary foods compared to the corn oil complementary foods; erythrocyte AA levels were significantly lower with consumption of the fatty fish complementary foods compared to the corn oil complementary foods. Erythrocyte and plasma ALA levels and erythrocyte EPA levels were significantly higher with consumption of the rapeseed complementary foods compared to the corn oil complementary foods; erythrocyte LA levels were significantly lower with consumption of the rapeseed complementary foods compared to the corn oil complementary foods. Overall, while consumption of complementary foods containing oily fish contributed to favorable shifts in DHA levels, consumption of the corn oil complementary foods had no adverse effects on growth.

Phytosterols in the Infant Diet

Typical Levels in Infant Formula

Vegetable oils are a source of plant sterols referred to as phytosterols. Phytosterols are present in all plant cells and are important structural components of plant cell membranes (Moreau et al., 2018). Similar in structure to cholesterol, plant sterols may occur free or conjugates bound via an ester bond or via a glycosidic linkage. The most abundant phytosterols in plants and the human diet are β-sitosterol, campesterol, and stigmasterol.

Vegetable oils have a long history of use in the fat blend of infant formulas, and therefore have provided a source of phytosterols in the infant diet. As previously reviewed, the concentration of total sterols in vegetable oils commonly used in infant formula fat blends range from approximately 200 to 2200 mg per 100 g oil (Table 2). Relative to other oils commonly used in infant formula, corn oil and rapeseed oil (i.e., canola oil) tend to contain the highest concentration of total sterols.

The concentration of total phytosterols in commercially available infant formula has been reported. In an examination of 13 commercially available infant formulas in European markets (Sweden, Spain, and Czech Republic), the concentration of total plant sterols was reported to be 3.11 to 5.00 mg per 100 mL sample, with β-sitosterol present in the highest concentration (1.82 to 3.01 mg per 100 mL), followed by campesterol (0.72 to 1.15 mg per 100 mL), stigmasterol (0.27 to 0.53 mg per100 mL), brassicasterol (0.14 to 0.28 mg per 100 mL), and sitostanol (0.03 to 0.14 mg per 100 mL) (Claumarchirant et al., 2015). All of the infant formulas examined contained vegetable oils as a source of lipid, and 10 of the 13 products contained rapeseed oil which is a concentrated source of phytosterols. Huisman and colleagues (1996) also examined phytosterols content of infant formulas. In this study of 10 commercially available milk-based infant formulas including 3 from the U.S. market, total phytosterol concentrations were reported at 5.3 to 11.9 mg per 100 mL (as reported in Claumarchirant et al., 2015), with β-sitosterol present in the highest concentration. Sterols, including phytosterols, are prone to oxidation under manufacturing conditions employed in food processing including the production of infant formula. Concentrations of 7-ketositosterol in commercial formulas have been reported to range from not detected to 4.1 mcg per g of lipid (Zunin et al., 1998).

Evaluation of Safe Intakes of Phytosterols by Official Bodies

The safety of phytosterol consumption has been considered by several authoritative bodies, and consumption of phytosterols has been concluded to be safe. In the U.S., the use of phytosterols and their esters as ingredients has been the subject of 14 GRAS notices to FDA closed between 2000 and 2014 (GRN Nos. 39, 48, 53, 61, 112, 176, 177, 181, 206, 250, 335, 387, 398, and 492). FDA responded to each of these notices with a letter of "no questions" regarding the GRAS status of the intended uses of phytosterols described in those notices. The GRAS conclusions were based on comprehensive reviews and evaluation of biological data, the metabolism of phytosterols, and pre-clinical and clinical evidence of safety. The potential presence of phytosterol oxidation products was considered in the GRAS determinations and levels were concluded to not present any safety concerns based on evidence demonstrating that phytosterol oxides are poorly absorbed (Hovenkamp et al., 2008) and are shown to be non-toxic and non-genotoxic in pre-clinical studies (Koschutnig et al., 2010). The most recent review and response from the FDA occurred in 2014 regarding GRN 492 in which the cumulative intake of phytosterols from its addition to various foods was estimated to be as high as 11.0 g/person/day (244 mg/kg bw/day) at the 90th percentile of intake. These GRAS conclusions do not include use in infant formula, but many intended uses of phytosterols include use in foods that may be consumed by infants or young children such as yogurts, fruit juice, cereals, or pastas at levels typically in the range of 0.5 to 2.0 g per serving. As detailed in GRN 398, the estimated intake of phytosterols by infants and children ages 0 to 2 years was 390 and 654 mg/kg bw/day at the mean and 90^{th} percentile exposures, respectively. FDA did not question the safety at these levels of intake.

In the U.S. the use of canola oil in the fat blend of infant formula was concluded to be GRAS and FDA responded with a letter of "no concern" regarding this conclusion (FDA 2012, GRN 425). In this notification (GRN 425), the available evidence on safety of phytosterol consumption by infants and young children was reviewed. The maximum intended use of canola oil was

estimated to provide intake of up to 16.2 mg/kg bw/day phytosterols for an extreme consumer of infant formula, and FDA did not question the safety at this level of intake (FDA 2012).

The safety of phytosterol consumption has also been considered by authoritative bodies outside the U.S. In Europe rapeseed oil enriched with phytosterols was approved by the European Food Safety Agency (EFSA) (EFSA 2005). The WHO/FAO Joint Expert Committee on Food Additives (JECFA) critically evaluated the safety of phytosterols and determined the acceptable daily intake (ADI) to be 0-40 mg/kg bw/day for phytosterols, phytostanols and their esters. JECFA conclude that dietary exposure to phytosterols and phytostanols would typically be within the ADI range of 0-40 mg/kg bw/day.

A review of the published literature (see Appendix D for terms) since the last safety review in a GRAS notification identified numerous clinical studies of phytosterols. Abstracts of the identified studies were reviewed and no studies suggested safety concerns not previously considered by regulatory bodies.

Studies of Phytosterol Intake from Infant Formulas

The literature provides limited data on phytosterols and infants, primarily from studies of plasma concentrations of phytosterols among infants consuming infant formula containing vegetable oils. A recent *in vitro* digestion study demonstrated that the bioaccessibility of total sterols from infant formula was 76% in formula containing only vegetable oils and 72% in formula containing vegetable oils, milk fat, and milk fat globule membranes, with lower bioaccessibility of plant sterols compared to cholesterol (Hamdan et al., 2018).

In a study of 26 infants ages 1 to 12 months, plasma phytosterol concentrations among infants consuming formula containing vegetable oils as a source of fat were approximately 9 mg per 100 mL compared with approximately 2 mg per 100 mL in infants consuming breast milk or cow's milk (Mellies et al., 1976a). Concentrations of specific phytosterols (β-sitosterol, campesterol, and stigmasterol) among infants consuming formulas were reported to be approximately 2 to 5 times concentrations in infants consuming milk. A study by the same investigators observed plant sterols accumulation in aortic tissues of 5 infants fed phytosterol-rich infant formula containing vegetable oil (Mellies et al., 1976b). Results from these trials suggest that absorption of phytosterols may be higher in infancy. In adults, absorption efficiency of phytosterols has been estimated at approximately 2% which is low relative to an estimated 50% absorption efficiency of cholesterol (summarized in Gylling and Simonen, 2015). The available evidence also indicates that tissue concentrations of phytosterols, phytostanols and cholesterol reflect serum concentrations with no selective accumulation of plant sterols (Gylling and Simonen, 2015).

In a recent study, the effects of phytosterol and cholesterol concentrations in formula on cholesterol absorption and endogenous synthesis were studied in neonatal piglets (Babawale et al., 2018). Thirty-two male piglets (7 days of age at baseline) were randomized to one of four formulas (8 piglets/group) containing concentrations of phytosterols and cholesterol consistent with concentrations in standard commercially available formulas or human milk, with low and high phytosterol concentrations of approximately 10 and 79 mg, respectively, and low and high concentrations of cholesterol of approximately 23 and 86 mg, respectively. Following intake of formula for 3 weeks, apparent cholesterol digestibility was examined in ileal digesta; and plasma

and liver samples were examined for cholesterol, phytosterols, and markers of cholesterol synthesis. Plasma and hepatic concentrations of phytosterols were higher in piglets fed the high phytosterol formulas compared to concentrations in animals fed the low phytosterol formulas, all though there was not difference in plasma total cholesterol concentrations among the four groups. Ileal cholesterol digestibility content was significantly increased in piglets fed high cholesterol formulas. The apparent ileal digestible cholesterol content in piglets consuming the low cholesterol, low phytosterol formula was elevated compared to the low cholesterol, high phytosterol formula though the difference was not statistically significant. Cholesterol precursor concentrations in plasma were lowest in piglets fed the high cholesterol, low phytosterol formula. Liver desmosterol-to-cholesterol ratio concentrations were lowest in piglets fed the low relative to high phytosterol formulas. Liver lasthosterol to cholesterol ratio was highest among the low cholesterol formula treatment groups, though the difference was only significantly greater among the low cholesterol, high phytosterol formula group compared to the other treatment groups. Overall, the results suggest that phytosterols in formula may inhibit cholesterol absorption and enhance cholesterol synthesis.

Gylling and colleagues analyzed cholesterol metabolism and ratios of serum non-cholesterol sterols to cholesterol in 96 children and adolescents ages 0 to 15 years without dyslipidemia (Gylling et al., 2018). The healthy population included 14 infants (<1 year), 37 children age 1-5 years, 24 children age 6-10 years, and 21 adolescents age 11-15 years. Breastfeeding status of the infants was not specified. Individual profiles of serum cholesterol and non-cholesterol sterols were reported to differ by age. Squalene and cholestenol, both markers of cholesterol synthesis, as well as desmosterol were elevated in infants compared with the other age groups, while the concentration of plant sterols including campesterol, stigmasterol, and avenasterol were lower compared to the older age groups. Cholesterol homeostasis was evident in children 1 year of age and older, and cholesterol absorption predominated cholesterol synthesis in children ages 1 to 10 years.

Studies of supplemental phytosterols in young children provide additional evidence of safety of phytosterol consumption. In a study of 40 young children (Tammi et al., 2001), 20 children were randomized to transition to a diet low in saturated fat and cholesterol and supplemented with 10-15 g of a vegetable oil or margarine (e.g., preferably low erucic acid rapeseed oil) at 1 year of age and 20 children were randomized to transition to cow's milk (1.9 to 2.9% milk fat) with no supplemental vegetable oil. Children randomized to consume vegetable oil consumed approximately twice the level of phytosterols consumed by children on the control diet. The diets were followed for 1 month; at 13 months of age, plasma sterol concentrations were increased approximately 60% in children randomized to increase consumption of vegetable oils. There was no difference in concentrations of serum cholesterol or cholesterol precursors between the groups (unadjusted and adjusted for cholesterol) with the exception of unadjusted desmosterol concentration, which was significantly higher among children in the vegetable oil supplementation group. These findings indicate that in children, phytosterol absorption was comparable to absorption observed in adults and intake has minimal effect on endogenous cholesterol synthesis. Garoufi and colleagues (2014) prospectively examined the effects of daily intake of 2 g of plant sterols in children ages 4.5 to 15.9 years with hypercholesterolemia in an open label study. Following daily intake of the plant sterols for a period of 6-12 months, levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, small density LDL-cholesterol,

non-high density lipoprotein (HDL) cholesterol, and apolipoprotein B (ApoB) were significantly lower in children after consuming plant sterols compared to baseline.

Vitamins

Corn oil is a source of naturally occurring vitamin E and vitamin K, both of which are fat soluble vitamins required in infant formula. Assuming 50% of calories are provided as fat in infant formula and corn oil accounts for a maximum of 3.0% of the fat blend, each 100 kcal of infant formula will contain no more than 0.17 g corn oil. The typical concentration of vitamin E (as α-tocopherol equivalent) in corn oil is 45.4 mg per 100 g and the typical concentration of vitamin K in corn oil is 17.6 μg per 100 g (Table 4), thus each 100 kcal of infant formula will contain approximately 0.08 mg vitamin E (0.11 IU vitamin E) and 0.03 μg vitamin K from corn oil.

Infant formula in the U.S. is required to provide a minimum of 0.7 IU vitamin E and 4 μg vitamin K per 100 kcal (21 CFR §107.100). The intended use of corn oil in infant formula will provide low levels of these vitamins relative to the required levels.

The Institute of Medicine has established a Tolerable Upper Intake Level (UL) for vitamin E, though a UL for infant populations was not determinable due to lack of data on adverse effects and concern regarding lack of ability to handle excess amounts (IOM 2000). The UL for vitamin E among children ages 1-3 years, the youngest age group for which a UL was established for this nutrient, is 200 mg vitamin E in any form of supplemental α-tocopherol. The IOM has not established for vitamin K for any age group and identification of a UL was concluded to be not determinable (IOM 2001).

Overall, the naturally occurring levels of vitamins E and K in corn oil are well below required levels of these vitamins in infant formula, and applicable ULs for young children, and therefore not a safety concern.

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 use of corn oil in infant formula has been established through consideration of the manufacture of the substance to ensure a food grade product, the physiological nature of the substance, and consideration of constituents in corn oil in the context of typical components in the infant diet. Clinical data from studies in which infants consumed infant formula and foods containing corn oil provide additional support for the safety of the intended use. The data and information on which the safety of the proposed use of corn oil in infant formula can be established are summarized below.

Corn oil is a food with a long history of use in the U.S. food supply and the FCC has established food grade specifications for corn oil in the U.S. food supply, including limits on fatty acids as well as physical and chemical properties of the oil. The corn oil intended for use in infant formula is produced under conditions of cGMP and meets specifications consistent with FCC specifications for corn oil.

Lipids in the form of triglycerides are the predominant source of energy for infants, accounting for approximately 50% of total energy intake. Infant formulas typically contain a blend of vegetable oils, potentially in combination with other fat sources, to achieve a fatty acid profile designed to mimic the fatty acid pattern of human milk because no single fat source replicates the pattern of fatty acids found in human milk. Commonly used vegetable oils in infant formula currently available in the U.S. include soy, high oleic safflower, high oleic sunflower, palm olein, palm, and coconut. Infants consuming the calorically dense exempt infant formula are term infants with a functional or partially functional gastrointestinal tract in the absence of comorbidities affecting metabolism and would be expected to handle fats, including corn oil, as would other term infants.

For an infant weighing 4.5 kg and consuming the calorically dense infant formula at a typical level of intake of 120 kcal/kg bw/day, the total daily intake of fat is approximately 6.7 g/kg

bw/day; the intended use of corn oil will provide 0.20 g corn oil/kg bw/day, or a total of 0.9 g corn oil. An infant consuming the formula at a high level of intake (175 kcal/kg bw/day) and weighing up to 9 kg is estimated to consume up to 2.6 g corn oil per day. The use of corn oil in infant formula at the maximum intended use of no more than 3.0% by weight in the fat blend will provide infants with fat in the form of triglycerides and contribute to the overall desired fatty acid profile in the formula. The predominant fatty acids in food-grade corn oil include linoleic acid, oleic acid, and palmitic acid, followed by stearic and linolenic acids, which collectively account for the more than 90% of corn oil by weight. These fatty acids are present in both breast milk and other oils commonly used in infant formula. The fatty acids provided by corn oil are thus common components in the infant diet and corn oil will be substitutional with other oils as a source of a small fraction (i.e., 3.0%) of the fatty acids in the fat blend. Intake of fatty acids arising from the addition of corn oil to infant formulas at the proposed use does not raise any safety concerns. The composition of the corn oil that is the subject of this GRAS review is consistent with that of typical corn oil.

Vegetable oils are typically a source of phytosterols. As shown in Table 3, the concentration of total sterols in corn oil samples representative of the oil that is the subject of this GRAS notification is 777 mg per 100 g oil. Relative to other oils commonly used in infant formula, corn oil along with low erucic acid rapeseed oil (i.e., canola oil) tend to contain higher concentrations of total sterols. Assuming the maximum intended use of 3.0% corn oil in the fat blend and a typical phytosterol concentration of 777 mg per 100 g corn oil, the corn oil fraction will contribute 1.3 mg phytosterols per 100 kcal formula. As previously shown in Table 10, infant formula consumed at a typical formula intake of 120 kcal/kg bw/day provides an estimated 1.6 mg phytosterols per kg bw/day, and formula intake at a level of 175 mL/kg bw/day, which represents a high intake, provides an estimated 2.3 mg phytosterols per kg bw/day. The JECFA ADI for phytosterols is 40 mg/kg bw/day; therefore, the intake of phytosterols from the maximum intended use of corn oil falls well below a level determined to be safe.

Because infant formula is reasonably the only source of nutrients for the target population, there is no need to account for background intake of phytosterols from dietary sources other than infant formula. However, other oils in the fat blend, for example canola oil, could potentially contribute additional phytosterols. The use of canola oil in term infant formulas at levels up to 31% of total fat blend was estimated to provide phytosterol intake of up to 16.2 mg/kg bw/day; intake of phytosterols at this level was determined to be GRAS as detailed in GRN 425 using the JECFA ADI of 40 mg/kg bw/day; FDA did not question this conclusion of safety (FDA 2012). Allowing for phytosterol intake of up to 16.2 mg/kg bw/day from the potential use of canola in the fat blend and the proposed maximum use of corn oil in the fat blend, corresponding to 2.3 mg phytosterols per kg bw/day for high intake of formula, results in total phytosterol intake of approximately18.5 mg/kg bw/day which remains below the ADI of 40 mg/kg bw/day. Intakes of phytosterols arising from the addition of corn oil to infant formulas at the proposed use therefore do not raise any safety concerns.

Corn oil is also a source of naturally occurring vitamins E and K. Representative samples of the corn oil that is the subject of this GRAS determination demonstrate the vitamin E (d-α-tocopherol equivalent) concentration of the oil is in the range of 42.7 to 48 mg per 100 g oil while the concentration of vitamin K1 is in the range of 12.9 to 20.2 μg per 100 g. The naturally occurring levels are well below required levels: for vitamin E, the mean contribution of 0.0.11 IU per 100 kcal from corn oil is below the minimum required concentration of 0.7 IU per 100 kcal

in infant formula, and for vitamin K, the mean contribution of 0.03 μg per 100 kcal from corn oil is below the minimum required concentration of 4 μg per 100 kcal in formula. The UL for vitamin E among children ages 1-3 years, the youngest age group for which a UL was established for this nutrient, is 200 mg vitamin E in any form of supplemental α-tocopherol. The IOM has not established for vitamin K for any age group and identification of a UL was concluded to be not determinable (IOM 2001). The intended use of corn oil does not present a safety concern with regard to vitamins E and K.

As previously noted, ingredient specifications are in place to ensure that the corn oil intended for use by infants meets relevant established limits for potential contaminants of concern, including metals, microorganisms (i.e., general and pathogenic, including *Salmonella* and *Enterobacteriaceae*), mycotoxins, dioxins and dioxin-like PCBs, non-dioxin-like PCBs, glycidyl fatty acid esters, polycyclic aromatic hydrocarbons (PAHs), pesticides, radioactivity, and solvents.

While not as widely used as some vegetable oils, corn oil is used in infant formulas globally and the literature documents that corn oil was commonly used in infant formulas in the U.S. as recently as the late 1990s. Data in the published literature report results from studies using commercially available infant formulas containing corn oil as a component of the fat blend. Not all studies were designed as safety studies, although information on infant growth, tolerance, and biochemical responses in these studies provide evidence on the suitability of corn oil as a component of the fat blend. Infant formula with corn oil accounting for 50% of the fat blend was demonstrated to support normal growth over a period of 8 weeks in a study of healthy term infants comparable to infants fed formula containing 60% soy oil in the fat blend or human milk with no effect on percentages of DHA in plasma or red blood cells compared to the soy oil formula (Ponder et al., 1992). Commercial infant formula based on corn oil (accounting for an unspecified percent of fat blend) designed for preterm infants also was demonstrated to support growth compared to formula based on soy oil in an intervention of infants from 30 to 57 weeks postconceptional age (Uauy et al., 1990; Uauy et al., 1994; Hoffman et al. 1999). Additional published and unpublished studies designed to examine the effect of infant formula on an aspect of efficacy or a metabolic parameter provide further evidence that fat blends containing corn oil support growth and lipid responses are consistent with expected responses based on the fatty acid profile (De Souza et al., 2018; Golawin and Pomeranze, 1962; Hayes et al., 1992; Leite et al., 2013; Schouten 2013). Studies monitoring consumption of corn oil in complementary foods provide corroborative evidence of the safety of intake of corn oil as a component of dietary fat in infants and very young children (Libuda et al., 2016; Schwartz et al., 2009).

Conclusion Regarding Safety and General Recognition of Safety

General recognition of safety through scientific procedures requires common knowledge throughout the scientific community knowledgeable about the safety of food ingredients that there is a reasonable certainty that a substance is not harmful under the intended conditions of use in foods. The aforementioned regulatory and scientific reviews related to the consumption and safety of corn oil as a component of the fat blend in exempt infant formula are published in

the scientific literature and, therefore, are generally available and generally known among the community of qualified food ingredient safety experts. There is broad-based and widely disseminated knowledge concerning corn oil and use of oils in the fat blend of infant formula. The data and publicly available information supporting the safety of the proposed maximum intended use of corn oil in exempt infant formula for term infants requiring a calorically dense formula and/or fluid restriction is 3.0% of the fat blend by weight as detailed in this document are not only widely known and disseminated, but are also commonly accepted among qualified food safety experts.

Discussion of Information Inconsistent with GRAS Determination

No information has been identified that would be inconsistent with a finding that the proposed use of corn oil in exempt infant formula, meeting appropriate specifications specified herein and used according to cGMP, is safe and GRAS.

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

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APPENDIX A

DNV·GL

MANAGEMENT SYSTEM CERTIFICATE

Certificate No:
198001-2016-FSMS-NLD-RvA

Initial date:
24 September 2015

Valid:
24 September 2018 - 24 September 2021

This is to certify that the management system of

[redacted]

has been assessed and determined to comply with the requirements of
FOOD SAFETY SYSTEM CERTIFICATION 22000

Certification scheme for food safety management systems consisting of the following elements: ISO 22000:2005, FSSC 22000 V4.1 - ISO TS 22002-1:2009 (Food) and additional FSSC 22000 requirements.

This certificate is applicable for the scope of:
Development and processing (pressing raw material, refining and modification) of vegetable oils, fats and margarine. - Category CIV.

The certification system consists of a minimum annual audit of the food safety management systems and a minimum annual verification of the PRP elements and additional requirements as included in the scheme and applicable technical specification for sector PRPs. Validity of this certificate can be verified in the FSSC 22000 database of certified organizations available on www.fssc22000.com.

Date of Certification Decision:
21 September 2018

Place and date:
Barendrecht, 24 September 2018

FSSC 22000

MGMT. SYS.
RvA C 024

For the issuing office:
DNV GL – Business Assurance
Zwolseweg 1, 2994 LB, Barendrecht,
The Netherlands

[redacted]

Erie Koek
Management Representative

DNV·GL

MANAGEMENT SYSTEM CERTIFICATE

Certificate No:
277926-2018-AQ-NLD-RvA

Initial certification date:
19 June 1995

Valid:
30 November 2018 - 30 November 2021

This is to certify that the management system of

[redacted]

has been found to conform to the Quality Management System standard:
ISO 9001:2015

This certificate is valid for the following scope:
Development, manufacturing and sales of vegetable oils, fats and industrial margarine including functional applications within the area of technical oils. Development, manufacturing and sales of fatty acids, feed fat, glycerol, feed and feed raw materials on vegetable basis.

Place and date:
Barendrecht, 01 November 2018

MEMBER OF MULTILATERAL RECOGNITION ARRANGEMENT IAF
MGMT. SYS.
RvA C 024

The RvA is a signatory to the IAF MLA

For the issuing office:
DNV GL - Business Assurance
Zwolseweg 1, 2994 LB Barendrecht,
The Netherlands

[redacted]

J.H.C.N. van Gijlswijk
Management Representative

APPENDIX B

[redacted]

[redacted]

Analytical Certificate / 80602887

Delivery	80602887
Your order no.	4502889531-4502857655P
Material	6280-648 CORN OIL HALAL
Customer material	10314108
Our reference	
Print date	2018-06-15
Date of Dispatch	2018-06-15

Batch 0001926400 / **Quantity** 1.710 KG / **Prod. date** 2018-05-02
Inspection lot 2065418

Characteristic	Result		Lower Limit	Target	Upper Limit
Colour Lovibond(Lovibond Tintometer)					
Colour 5 1/4" Yellow	6,0				20,0
Colour 5 1/4" Red	0,8				2,0
Fatty acid composition(IUPAC 2.304)					
Fatty acid composition C12:0	< 0,1	%			0,3
Fatty acid composition C16:0	11,3	%	9,0		13,0
Fatty acid composition C18:0	2,0	%	1,0		3,0
Fatty acid composition C18:1	32,5	%	24,0		42,0
Fatty acid composition C18:2	51,7	%	49,0		62,0
Fatty acid composition C18:3	1,3	%			2,0
Peroxide value(AOCS Cd 8b-90(m))					
Peroxide value	0,1	meq/kg			0,5
Flavour(Sensoric)					
Flavour	Approved				
Iodine value Wijs(IUPAC 2.205(m))					
Iodine value Wijs	122		118		128
Free fatty acids(IUPAC 2.201(m))					
Free fatty acids 282	0,04	%			0,10

[redacted]

[redacted]

[redacted]

[redacted]

Analytical Certificate / 80602887

Delivery	80602887
Your order no.	4502889531-4502857655P
Material	6280-648 CORN OIL HALAL
Customer material	10314108
Our reference	
Print date	2018-06-15
Date of Dispatch	2018-06-15

Batch 0001941815 / **Quantity** 2.090 KG / **Prod. date** 2018-06-13
Inspection lot 2088037

Characteristic	Result		Lower Limit	Target	Upper Limit
Colour Lovibond(Lovibond Tintometer)					
Colour 5 1/4" Yellow	4,7				20,0
Colour 5 1/4" Red	0,5				2,0
Fatty acid composition(IUPAC 2.304)					
Fatty acid composition C12:0	< 0,1	%			0,3
Fatty acid composition C16:0	11,6	%	9,0		13,0
Fatty acid composition C18:0	2,1	%	1,0		3,0
Fatty acid composition C18:1	32,8	%	24,0		42,0
Fatty acid composition C18:2	51,2	%	49,0		62,0
Fatty acid composition C18:3	1,1	%			2,0
Peroxide value(AOCS Cd 8b-90(m))					
Peroxide value	< 0,1	meq/kg			0,5
Flavour(Sensoric)					
Flavour	Approved				
Iodine value Wijs(IUPAC 2.205(m))					
Iodine value Wijs	122		118		128
Free fatty acids(IUPAC 2.201(m))					
Free fatty acids 282	< 0,01	%			0,10

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[redacted]

[redacted]

[redacted]

Analytical Certificate / 80616743

Delivery	80616743
Your order no.	4502918030-4502905376
Material	6280-648 CORN OIL HALAL
Customer material	10314108
Our reference	
Print date	2018-07-23
Date of Dispatch	2018-07-23

Batch 0001956365 / **Quantity** 3.800 KG / **Prod. date** 2018-07-16
Inspection lot 2106515

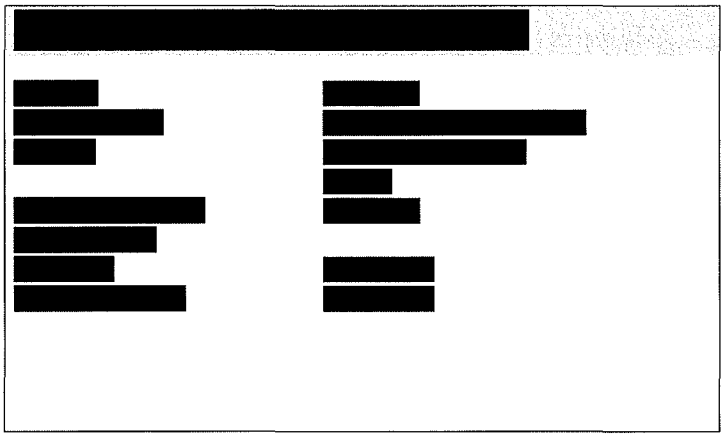
Characteristic	Result		Lower Limit	Target	Upper Limit
Colour Lovibond(Lovibond Tintometer)					
Colour 5 1/4" Yellow	6,8				20,0
Colour 5 1/4" Red	1,0				2,0
Fatty acid composition(IUPAC 2.304)					
Fatty acid composition C12:0	< 0,1	%			0,3
Fatty acid composition C16:0	12,0	%	9,0		13,0
Fatty acid composition C18:0	2,3	%	1,0		3,0
Fatty acid composition C18:1	30,8	%	24,0		42,0
Fatty acid composition C18:2	52,6	%	49,0		62,0
Fatty acid composition C18:3	1,2	%			2,0
Peroxide value(AOCS Cd 8b-90(m))					
Peroxide value	< 0,1	meq/kg			0,5
Flavour(Sensoric)					
Flavour	Approved				
Iodine value Wijs(IUPAC 2.205(m))					
Iodine value Wijs	122		118		128
Free fatty acids(IUPAC 2.201(m))					
Free fatty acids 282	0,02	%			0,10

[redacted]

[redacted]

[redacted]

[redacted]



Batch 0001981011 / **Quantity** 3.800 KG / **Prod. date** 2018-09-25
Inspection lot 2145966

Characteristic	Result		Lower Limit	Target	Upper Limit
Colour Lovibond(Lovibond Tintometer)					
Colour 5 1/4" Yellow	6,2				20,0
Colour 5 1/4" Red	0,9				2,0
Fatty acid composition(IUPAC 2.304)					
Fatty acid composition C12:0	< 0,1	%			0,3
Fatty acid composition C16:0	11,6	%	9,0		13,0
Fatty acid composition C18:0	2,3	%	1,0		3,0
Fatty acid composition C18:1	33,1	%	24,0		42,0
Fatty acid composition C18:2	50,6	%	49,0		62,0
Fatty acid composition C18:3	1,1	%			2,0
Peroxide value(AOCS Cd 8b-90(m))					
Peroxide value	< 0,1	meq/kg			0,5
Flavour(Sensoric)					
Flavour	Approved				
Iodine value Wijs(IUPAC 2.205(m))					
Iodine value Wijs	121		118		128
Free fatty acids(IUPAC 2.201(m))					
Free fatty acids 282	0,02	%			0,10

[redacted]

Table Appendix B-1. Fatty acid analysis of corn oil samples (internal data)

Fatty Acid	Specification (%)			Results by Sample Code (%)				
	Current GRAS							
	Min	Max	FCC 11	12997335	1803331	1917272	Mean	Range
<C14			<0.1	0.01	0.44	0.15	0.20	0.01 - 0.44
C14:0		0.3	<1.0	0.08	0.15	0.06	0.10	0.06 - 0.15
C16:0	9	13	8.0-19.0	11.25	11.46	10.43	11.05	10.43 - 11.46
C16:1			<0.5	0.10	0.11	0.10	0.10	0.1 - 0.11
C18:0	1	3	0.5-4.0	2.07	2.06	2.33	2.15	2.06 - 2.49
C18:1*	24	42	19-50	33.35	33.03	32.50	32.96	32.5 - 33.35
C18:2*	49	62	38-65	50.29	49.38	51.39	50.35	49.38 - 51.39
C18:3*		2	<2.0	1.01	0.94	1.24	1.06	0.94 - 1.24
C20:0			<1.0	0.44	0.41	0.43	0.43	0.41 - 0.44
C20:1			<0.5	0.31	0.44	0.41	0.39	0.31 - 0.44
C22:0			<0.3	0.18	0.17	0.15	0.17	0.15 - 0.18
C22:1			<0.1	0.03	0.04	0.08	0.05	0.03 - 0.08
C24:0			<0.4	0.21	0.17	0.16	0.18	0.16 - 0.21

Values include sum of individual forms:
C18:1 = sum of C18:1w7 and C18:1w9
C18:2 = sum of C18:2w6 and C18:2 conjugated
C18:3 = sum of C18:3w3 and C18:3w6
Values reported as < 0.02 (limit of quantification; LOQ) were replaced with 0.01 (LOQ/2) to calculate summary statistics.

[redacted]

Unsaponifiable Matter Corn oil (material 6280)			
Batch no:	2017017	2023678	2028874
Lot no:	2192057	2201158	2209780
Lot date:	2018-12-14	2018-01-03	2018-01-18
Unsaponifiable matter (%):	1.0	1.0	1.1

19-02-2019

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Sterol composition of Corn oil (628000)			
Batch no:	2017017	2023678	2028874
Lot no:	2192057	2201158	2209780
Lot date:	2018-12-14	2018-01-03	2018-01-18
Total Sterols	800 mg/100g	750 mg/100g	780 mg/100g
Campesterol	20.6 %	20.3 %	20.4 %
Campestanol	0.9 %	0.7 %	0.9 %
Stigmasterol	6.7 %	7.3 %	6.9 %
Sitostanol	2.6 %	2.1 %	2.4 %
Beta-sitosterol	62.5 %	64.4 %	64.0 %
Delta5-avenasterol	2.0 %	2.8 %	2.7 %
Delta7-stigmasterol	0.3 %	0.1 %	0.2 %
Delta7-avenasterol	1.5 %	1.2 %	1.2 %

01-03-2019

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Appendix C. Contaminant Specifications and Analytical Data

APPENDIX C

General Information:

Sample No.:	171104892
Sample:	corn oil 1952283
Date of receipt:	16.10.2017
Testing period (begin / end):	16.10.2017 / 24.10.2017
Quantity:	621g
Packaging:	Plastic can

Test Results:

Parameter	Method	Lab	Unit	Result	Limit of quantification	Requirements
Minerals/metals:						
Lead	DIN EN 15763, mod.	HH	mg/kg	< 0,01	0,01	
Cadmium	DIN EN 15763, mod.	HH	mg/kg	< 0,005	0,005	
Mercury	DIN EN 15763, mod.	HH	mg/kg	< 0,01	0,01	
Arsenic	DIN EN 15763, mod.	HH	mg/kg	< 0,02	0,02	
Iron	DIN EN 15763, mod.	HH	mg/kg	< 0,20	0,20	
Copper	DIN EN 15763, mod.	HH	mg/kg	< 0,05	0,05	
Nickel	DIN EN 15763, mod.	HH	mg/kg	< 0,05	0,05	
Tin	DIN EN 15765, mod.	HH	mg/kg	< 0,05	0,05	
Aluminium	DIN EN 15763, mod.	HH	mg/kg	0,28	0,10	
Chromium	DIN EN 15763, mod.	HH	mg/kg	< 0,04	0,04	

Mycotoxins:						
Ochratoxin A	ASU L 00.00-50a(EG), SOP M1386, LC-MS/MS	HH	µg/kg	< 0,5	0,5	
Deoxynivalenol (DON)	SOP M 2021, LC-MS/MS	HH	µg/kg	< 50	50	
Zearalenone	SOP M 2021, LC-MS/MS	HH	µg/kg	< 10	10	

Mycotoxins:						
Aflatoxin B1	SOP M 2087, LC-MS/MS	HH	µg/kg	< 0,01	0,01	
Aflatoxin B2	SOP M 2087, LC-MS/MS	HH	µg/kg	< 0,01	0,01	
Aflatoxin G1	SOP M 2087, LC-MS/MS	HH	µg/kg	< 0,01	0,01	
Aflatoxin G2	SOP M 2087, LC-MS/MS	HH	µg/kg	< 0,01	0,01	
Sum Aflatoxins B/G	calculated	HH	µg/kg	< 0,01		

Erstellt: 24.10.2017 i.A. Saskia Schock Customer Service Consultant Agriculture.
Freigegeben: 24.10.2017 i.V. Larissa Münzberg Customer Service Consultant Agriculture.

Sample 171104892	corn oil 1952283					
Parameter	Method	Lab	Unit	Result	Limit of detection	Requirements

Parameter	Method	Lab	Unit	Result	Limit of detection	Requirements
Microbiological analysis:						
Total Viable Count	DIN EN ISO 4833-1 / PCA / 30°C/72h	HH	cfu/g	< 100	100	
Yeasts (incl. osmophilic yeasts)	ISO 21527-2 / DG18 / 25°C/120h	HH	cfu/g	< 10	10	
Moulds (incl. xerophilic moulds)	ISO 21527-2 / DG18 / 25°C/120h	HH	cfu/g	< 10	10	
Enterobacteriaceae	DIN ISO 21528-1 mod. / VRBD / 37°C/22h	HH	in 10 g	negative		
Cronobacter spp. (Enterobacter sakazakii)	ISO/TS 22964 mod. / BPW / 37°C/18h / mLST / 44°C/24h / ESIA / 44°C/24h	HH	in 10 g	negative		
Coliform bacteria	ISO 4831 / LST / 37°C/24h / Brila / 37°C/48h	HH	in 1 g	negative		
E. coli	DIN EN ISO 16649-3 / MGM 37°C/22h / TBX 44°C/20h	HH	in 1 g	negative		
Coagulase-positive-staphylococci	DIN EN ISO 6888-2 / RPF / 37°C/45h	HH	cfu/g	< 10	10	
Clostridium perfringens	DIN EN ISO 7937 / TSC / 37°C/20h	HH	cfu/g	< 10	10	
Salmonella spp.	DIN EN ISO 6579	HH	in 25 g	negative		
Listeria monocytogenes	DIN EN ISO 11290-1 mod.(1)	HH	in 25 g	negative		

(1) Modifications according to AFNOR BRD 07 / 16-01 / 09 / AFNOR BRD 07 / 04-09 / 98/022 NordVal

The laboratory sites of the SGS group Germany according to the abbreviations mentioned above are listed at http://www.institut-fresenius.de/filestore/89/laborstandortkuerzelsgs2.pdf.

*** End of test report ***

[redacted]

To whom it may concern

STATEMENT CONCERNING CONTAMINANTS FOR OILS AND FATS FOR INFANT NUTRITION

This document states the maximum residual levels (MRL) of contaminants in fully refined vegetable oils and fats for infant nutrition, which are delivered from [redacted], with reference to relevant EU legislation, WHO Codex Alimentarius Codex Stan, MVO (Product Boards for Margarine, Fats and Oils) "Specification for Refined Vegetable and Marine Oils excluding Olive Oil" and FEDIOL Code of Practices. MRLs based on legislation in bold text in the tables below.

[redacted] overall food safety system is based on risk analysis (HACCP) of the entire supply chain. In the monitoring program raw materials, additives and final products are regularly sampled and analysed according to a schedule, and analytical results for potential contaminants are monitored. This program is a part of and serves as a supplementary check on the effectiveness of the food safety system.

The statement concerns:

Dioxins, furans, dioxin-like PCBs	Microorganisms	Pesticides
Non dioxin-like PCBs	Mineral Oils	Radio activity
Glycidyl Fatty Acid Esters	Mycotoxins	Solvents
Metals	PAHs	

Dioxins and dioxin-like PCBs

Component	**MRL according to AAK standard (pg/g fat)**	**MRL according to standard**	**Reference**
Sum of dioxins (WHO-PCDD/F-TEQ)	0.3	**Oils: 0.75 pg/g fat Infant food: 0.1 pg/g wet weight**	EU Regulations 1259/2011, 1881/2006
Sum of dioxins and dioxin-like PCB's (WHO-PCDD/F-PCB-TEQ)	0.5	**Oils: 1.25 pg/g fat Infant food: 0.2 pg/g wet weight**	EU Regulations 1259/2011, 1881/2006

Non dioxin-like PCBs

Component	**MRL according to AAK standard (ng/g fat)**	**MRL according to standard**	**Reference**
Sum of PCB28, PCB52, PCB101, PCB138, PCB153, PCB180	1.0	**Oils: 40 ng/g fat Infant food: 1.0 ng/g wet weight**	EU Regulations 1259/2011, 1881/2006

[redacted]

[redacted]

Glycidyl Fatty acid esters

Component	MRL according to AAK standard (µg/kg)	MRL according to standard (µg/kg)	Reference
Glycidyl fatty acid esters expressed as glycidol	300	**Oils: 1000** **Oils destined for baby food and processed cereal-based food: 500** **Infant food:** **75 on powder formulations** **10 on liquid ready to use formulations**	EU Regulations 2018/290, 1881/2006

Metals

Component	MRL according to AAK standard (mg/kg)	MRL according to standard (mg/kg)	Reference
Aluminium (Al)	0.5	-	AAK Standard
Arsenic (As)	0.1	0.1	WHO Codex Alimentarius Codex Stan 210
Cadmium (Cd)	0.005	Oils: - **Soya beans: 0.2** **Infant food: 0.005**	EU Regulations 488/2014, 629/2008, 1881/2006
Copper (Cu)	0.05	0.05	MVO
Iron (Fe)	0.5	0.5	MVO
Lead (Pb)	0.01	**Oils: 0.1** **Infant food: 0.01**	EU Regulations 2015/1005, 1881/2006
Mercury (Hg)	0.01	**Oil seeds: 0.02** **Infant food: 0.01**	EU Regulation 396/2005 including amendments
Nickel (Ni)	0.2	0.2	MVO
Tin (Sn)	50	Oils: - **Infant food: 50**	EU Regulation 1881/2006

[redacted]

[redacted]

Microorganisms

The deodorisation step, in which the oil is heated to above 200°C under vacuum, effectively eliminates microbiological activity.

Indicator organism	MRL according to AAK standard	MRL according to standard	Reference
General			
Total plate count	100 cfu/g	-	AAK Standard
Yeast	10 cfu/g	10 cfu/g	MVO
Mould	10 cfu/g	10 cfu/g	MVO
Enterobacteriaceae	Absent in 10 g	Oils: - **Infant food: Absent in 10 g**	EU Regulations 1441/2007, 2073/2005
Pathogenic			
Listeria monocytogenes	Absent in 25 g	Oils: - **Infant food: Absent in 25 g**	EU Regulations 1441/2007, 2073/2005
Salmonella	Absent in 25 g	Oils: - **Infant food: Absent in 25 g**	EU Regulations 1441/2007, 2073/2005
Cronobacter sakazaki (former Enterobact. sakazaki)	Absent in 10 g	Oils: - **Infant food: Absent in 10 g**	EU Regulations 1441/2007, 2073/2005
E. coli	Absent in 1 g	.	AAK Standard
Bacillus cereus	50 cfu/g	Oils: - **Infant food: 50 cfu/g**	EU Regulations 1441/2007, 2073/2005

Mineral Oils

Component	MRL according to AAK standard (mg/kg)	MRL according to standard (mg/kg)	Reference
Mineral oils/Diesel/Long chain hydrocarbons Range C10-C56	50	-	AAK Standard

Mycotoxins

Component	MRL according to AAK standard (µg/kg)	MRL according to standard (µg/kg)	Reference
Aflatoxin, B1	0.10	Oils: - **Infant food: 0.10**	EU Regulations 165/2010, 1881/2006
Ochratoxin A	0.50	Oils: - **Infant food: 0.50**	EU Regulation 1881/2006
Deoxynivalenol	200	Oils: - **Infant food: 200**	EU Regulations 1126/2007, 1881/2006
Zearalenon	20	**Infant food: 20**	EU Regulations 1126/2007, 1881/2006
Fumonisins (sum of B1 + B2)	200	**Infant food: 200**	EU Regulations 1126/2007, 1881/2006

[redacted]

[redacted]

Polycyclic Aromatic Hydrocarbons (PAHs)

Component	MRL according to AAK standard (µg/kg)	MRL according to standard (µg/kg)	Reference
Bens(a)pyrene (BaP)	1.0	**Oils: 2.0** **Infant food: 1.0**	EU Regulation 835/2011
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	2.0	**Oils: 10** **Infant food: 1.0**	EU Regulation 835/2011

Pesticides

Component	MRL according to AAK standard (mg/kg)	MRL according to standard (mg/kg)	Reference
Organochlorine and organophosphorus pesticides	Depending on the type of pesticide: 0.003-0.01 per pesticide For complementary information, see AAK statement "Statement concerning pesticides for oils and fats for infant nutrition"	**Oils seeds and fruits: 0.01-0.1 per pesticide, depending on the raw material and type of pesticide** **Infant food: 0.003-0.01 per pesticide, depending on the type of pesticide**	EU Regulations 600/2010, 839/2008, 149/2008, 396/2005 EU Regulation 609/2013 EU Directive 2006/141

Radio activity

Isotops	MRL according to AAK standard (Bq/kg)	MRL according to standard (Bq/kg)	Reference
$Cs^{134} + Cs^{137}$	370	**Oils: 600** **Infant food: 370**	EU Regulation 733/2008

[redacted]

[redacted]

Solvents

Component	MRL according to AAK standard (mg/kg)	MRL according to standard (mg/kg)	Reference
Acetone	1	-	AAK Standard
Hexane	1	**1**	EU Directive 2009/32
Methanol	10	**10**	EU Directive 2009/32

Yours faithfully,

[redacted]

[redacted]

[redacted]

28-02-2019

To whom it may concern

Statement regarding Corn oil [redacted]

With reference to above-mentioned product, Residual Solvents including Acetone, Hexane and Methanol, comply with the maximum limits permitted for vegetable oils for food and infant formula according to EU Directive 2009/32 (1mg/kg, 1mg/kg and 10mg/kg respectively).
Solvents are measured as part of [redacted] contaminants monitoring programme for oils and fats for infant nutrition. Results show levels below detection limit of the analytical method (<0,5mg/kg).

[redacted]

[redacted]

[redacted]

28-02-2019

To whom it may concern

Statement regarding Corn oil from [redacted]

With reference to above-mentioned product, Fumonisins (sum of B1 + B2) complies with the maximum limit (200µg/kg) permitted for vegetable oils for food and infant formula according to EU legislation 1881/2006.
Fumonisins are measured as part of [redacted] contaminants monitoring programme for oils and fats for infant nutrition. Results show levels below detection limit of the analytical method (<50µg/kg).

[redacted]

[redacted]

Appendix D. PubMed Literature Searches

Date	Search Terms	Citations
31-Jul-18	Search (infant formula) AND ("corn oil" OR sterol OR phytosterol) Filters: English	250
31-Jul-18	Search ("Phytosterols"[Mesh]) AND ("Corn Oil"[Mesh] OR "corn oil") Filters: English	32
7-Jan-19	Search "infant formula" AND (fat or lipid) AND (source or quality) Sort by: Best Match Filters: published in the last 10 years; English	96
10-Jan-19	Search phytosterol AND infant Sort by: Best Match Filters: English	61
13-Jan-19	Search ("corn oil" OR "maize oil") AND infant Sort by: Best Match Filters: English	76
10-Feb-19	Search (phytosterol OR plant sterol) AND (children OR child) Filters: English	177
3-Mar-19	Search (infant OR newborn OR formula) AND ("corn oil" OR "maize oil") Filters: Humans; English	87
20-Oct-19	Search phytosterol Filters: Clinical Trial; Publication date from 2012/01/01; English	124
20-Oct-19	Search phytosterol AND toxicity Filters: Publication date from 2012/01/01; English; Field: Title/Abstract	13

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

Hogan Lovells US LLP
Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

Tel: +1 202 637 5600
Direct: +1 202 637 6986
Mobile +1 979-422-7860
Fax: +1 202 637 5910
Email: xin.tao@hoganlovells.com
www.hoganlovells.com

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

From:	Tao, Xin
To:	Morissette, Rachel
Cc:	Steinborn, Steven B.; Harry, Molly; Hall, Karen
Subject:	RE: request for teleconference to discuss GRNs 898, 899, and 900
Date:	Friday, May 1, 2020 5:42:04 PM
Attachments:	image001.png Response to U.S. Food and Drug Administration (FDA)'s Question on Intended Use for GRAS Notices 898, 899, and 900.pdf

Dear Rachel,

Attached, please find our response to the over-arching question regarding the subpopulation. It 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.

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

Best regards,
Steve and Xin

Xin Tao
Senior Associate

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Columbia Square
555 Thirteenth Street, NW
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Tel: +1 202 637 5600
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Fax: +1 202 637 5910
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www.hoganlovells.com

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Friday, April 24, 2020 2:20 PM
To: Tao, Xin
Cc: Steinborn, Steven B.; Harry, Molly; Hall, Karen
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin and Steven,

Thank you again for meeting with us today. We all felt it was a very productive discussion. As mentioned, we'll be expecting to see your response to our over-arching question first regarding the subpopulations for GRN 898-900. If you can have that response to us as soon as possible (within 10 business days), we will be able to continue our reviews and will be generating an additional set of questions for each notice. You can expect to receive copies of those questions from Molly, Karen, and myself as the project managers of the three notices. In the meantime, please let us know if you have any further questions.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Friday, April 24, 2020 11:49 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel – Here is an updated version with one typo fixed on Slide #8. Sorry about that.

Regards,
Xin

From: Tao, Xin
Sent: Friday, April 24, 2020 11:46 AM
To: 'Morissette, Rachel'
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

That would be great if you can lead the meeting and advance the slides Rachel. Sorry for the delay on our end, and yes, our plan is to go through them very quickly with the agency on the call and please note we plan to stop at Slide #8 for the quick presentation. The remaining slides are backup slides just in case we need to reference them during the discussion with the agency.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Friday, April 24, 2020 11:41 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Thank you. We will not have a chance to fully review these in time for the meeting, but I sent them

to the review team to take a look in case they are able to review them. I can share my screen when the time comes and advance the slides for you. I will give some introductory remarks and then ask you to briefly go through the slides. We want to spend as much time as possible on the discussion.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Friday, April 24, 2020 11:25 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900
Importance: High

Dear Rachel,

Attached, please find our short presentation (10-15 mins) to provide clarification on the infant subpopulation. Please note we also have one more attended and the following is the final list for your easy reference:

- Miguel Del Toro, Danone North America/Nutricia North America
- Madeline Jurch, Danone North America/Nutricia North America
- Caitlin Krekel, Danone North America/Nutricia North America
- Nga Tran, Exponent
- Mary Murphy, Exponent
- Steve Steinborn, Hogan Lovells
- Xin Tao, Hogan Lovells

We look forward to our call.

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Tuesday, April 21, 2020 9:39 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin,

The following staff were invited to the meeting, though not all have accepted it yet. I won't know for sure until the meeting starts who will be able to join us, but this gives you an idea.

- Rachel Morissette, Ph.D. – Regulatory Review Scientist (RRS), Office of Food Additive Safety (OFAS)/Division of Food Ingredients (DFI)
- Molly Harry, M.S. – RRS, OFAS/DFI
- Karen Hall, M.S. – RRS, OFAS/DFI
- Sue Anne Assimon, Ph.D. – Toxicologist, OFAS/DFI
- Kotaro Kaneko, Ph.D. – Toxicologist, OFAS/DFI
- Danica DeGroot, Ph.D. – Toxicologist, OFAS/DFI
- Alison Edwards, Ph.D. – Chemist, OFAS/DFI
- Jeremy Mihalov, M.S. – Chemist, OFAS/DFI
- Perry Wang, Ph.D. – Chemist, OFAS/DFI
- Shayla West-Barnette, Ph.D. – Regulatory Review Team Lead, OFAS/DFI
- Negash Belay, Ph.D. – Regulatory Review Team Lead, OFAS/DFI
- Supratim Choudhuri, Ph.D. – Toxicology Team Lead, OFAS/DFI
- Janet Zang, Ph.D. – Toxicology Team Lead, OFAS/DFI
- Jannavi Srinivasan, Ph.D. – Chemistry Team Lead, OFAS/DFI
- Diana Doell, Ph.D. – Chemistry Team Lead, OFAS/DFI
- Megan Kulas – Consumer Safety Officer, Office of Nutrition and Food Labeling (ONFL)/Infant Formula and Medical Foods Staff (IFMFS)
- Carrie Assar, Pharm. D. – Team Lead, ONFL/IFMFS
- Andrea Lotze, M.D. – Medical Director, ONFL/IFMFS

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 6:29 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

As promised, following is the list of attendees and their afflation from our end for the Friday meeting:

- Miguel Del Toro, Danone North America/Nutricia North America
- Madeline Jurch, Danone North America/Nutricia North America
- Nga Tran, Exponent
- Mary Murphy, Exponent
- Steve Steinborn, Hogan Lovells
- Xin Tao, Hogan Lovells

If possible, could you please provide a list of FDA attendees so we can be better prepared?

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 12:19 PM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Sure, that would be fine.

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 12:11 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Rachel,

We received your invitation, and yes, we will provide a list of attendees and affiliations shortly.

Quick question: can we present a couple of slides to guide the subpopulation discussion during the call using WebEx? We can send them to you before the call as well.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 11:58 AM
To: Tao, Xin; Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Please let me know if you didn't receive the WebEx info. Also, please send me a list of attendees and affiliations the day before the meeting.

Thanks,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 11:45 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Great, thanks!

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 11:43 AM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Hi Xin,

It looks like that slot is still available. I'll send you a meeting invite with call-in info shortly.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 10:56 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Thank you, and I will call you at 11:30 am.

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 10:49 AM
To: Tao, Xin
Cc: Steinborn, Steven B.

Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Xin,

Yes, I'm available from 11:15 am-3 pm today. My desk number is 240-402-1212.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Monday, April 20, 2020 10:14 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

May I give you a quick call today at your convenience to discuss the meeting?

Regards,
Xin

Xin Tao
Senior Associate

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Columbia Square
555 Thirteenth Street, NW
Washington, DC 20004

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From: Tao, Xin
Sent: Monday, April 20, 2020 8:44 AM
To: 'Morissette, Rachel'
Cc: Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Thank you for the reminder. Sorry for the delay as we are trying to make sure we have the right people to attend the requested meeting and have been coordinating on our end. I will get back to you today.

Best regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, April 20, 2020 8:35 AM
To: Tao, Xin; Steinborn, Steven B.
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Steve and Xin,

I have not received a list of meeting dates that would work for you as of yet; therefore, I cannot guarantee that the options I listed below are still available. Due to the 180-clock for a GRAS notice review, we are requesting to have this meeting as soon as possible to ensure we can meet that deadline and move forward with our review of these three notices. Please let me know by COB today, if at all possible. You might also suggest some dates and times next week that could work in the event that the options I presented last week are no longer available.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Morissette, Rachel
Sent: Wednesday, April 15, 2020 11:16 AM

To: Tao, Xin <xin.tao@hoganlovells.com>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Thank you. The more options you can provide, the easier it will be to accommodate.

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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Office of Food Additive Safety
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rachel.morissette@fda.hhs.gov

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Wednesday, April 15, 2020 10:54 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: request for teleconference to discuss GRNs 898, 899, and 900

Dear Rachel,

Here is to acknowledge the receipt of your email. I will coordinate on our end and get back to you with our preferred date. Thank you!

Regards,
Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Wednesday, April 15, 2020 9:47 AM
To: Steinborn, Steven B.; Tao, Xin
Subject: request for teleconference to discuss GRNs 898, 899, and 900

Dear Steve and Xin,

We have reviewed your GRAS notices GRNs 000898, 000899, and 000900 for the intended use of dried milk fat, citric acid esters of mono- and diglycerides, and corn oil, respectively, in exempt infant

formulas for “term infants requiring a calorically dense formula and/or fluid restriction.” We request a teleconference with you to discuss all three notices. To provide some context, the over-arching question we have is to clarify the sub-population of term infants that may consume calorically dense or fluid restrictive infant formula. The rest of the discussion hinges on the answer to this question, as we have other issues that depend on clarifying the intended use and infant population. Please let me know if you are available for a teleconference during any of the following 1.5 hour slots. Since this teleconference involves three different notices and three different review teams, I’ve been asked to take the lead in coordinating this meeting as our office’s infant formula liaison to the Infant Formula and Medical Foods Staff in the Office of Nutrition and Food Labeling, who will also be attending the meeting. This is the group that administers the 412 Infant Formula submission process.

Monday April 20th 2-3:30 pm

Wednesday April 22nd 12-1:30 pm

Thursday April 23rd 9-10:30 am

Thursday April 23rd 9:30-11 am

Friday April 24th 9-12 pm

Friday April 24th 1-4 pm

If these dates don’t work, I can look into the following week, as well. Please note that schedules fill up very quickly for us, so please let me know as soon as possible your availability so we can secure a time.

Thank you for your attention to this matter.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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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.

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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
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+1 202-637-5969

Xin Tao
Xin.tao@hoganlovells.com
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Cc:

Molly A. Harry
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Karen M. Hall
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From:	Tao, Xin
To:	Morissette, Rachel
Cc:	Steinborn, Steven B.
Subject:	RE: additional questions for GRN 000900 - corn oil
Date:	Thursday, June 11, 2020 6:03:56 PM
Attachments:	image001.png Attachment B.PDF Attachment C.PDF Attachment D.PDF HL Response to FDA Additional Questions for GRN 900.pdf Attachment A.PDF

Dear Rachel,

Hope you keep doing well. Attached, please find our response to the agency's additional questions for GRN 000900. Please note that our response and attachments contain confidential commercial and trade secret information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. In accordance with FDA's implementing regulations, if a request for disclosure is received, we would like to ask that we be notified and provided an opportunity to address why the information or materials should not be released.

We would like to thank you again for the flexibility on the timeline. We trust our response addresses all the questions raised by the agency. 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.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

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From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Wednesday, May 13, 2020 11:26 AM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: additional questions for GRN 000900 - corn oil

Dear Mr. Steinborn,

Please see attached our additional questions for GRN 000900 based on your response to our overarching subpopulation question from May 1, 2020. Please let me know if you have any questions at this time. We request a response within 10 business days.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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Via Electronic Mail

June 11, 2020

Rachel Morissette, Ph.D.
Regulatory Review Scientist
Division of Food Ingredients
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Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

Re: Response to FDA's Questions for GRN 000900

Dear Dr. Morissette,

We hereby submit our responses to FDA's questions for GRN 000900, which covers the intended use of corn oil as a source of fat 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 Intended Use (Chemistry):

- ***FDA Question #1a****: Calorically-dense or energy dense formulas are not defined in the notice or in FDA's regulations.*

  1) For the purpose of the notice, does this term refer to infant formulas with 24 kcal per oz (81 kcal/100 mL) and above or are they specifically 100 kcal/100mL?

  2) Please clarify the range of energy densities for infant formulas that meet your definition of calorically-dense infant formulas.

Response to Question 1a: We hereby clarify that for purposes of GRAS Notice 000900 (GRN 900), the term "calorically-dense or energy dense formulas" refers specifically to formulas that provide 100 kcal/100mL. In other words, calorically-dense or energy dense formulas that target energy densities other than 100 kcal/100mL are not the subjects of this notification.

- ***FDA Question #1b****: In your dietary exposure estimate, you note that fat is typically 50% of energy in infant formula and that 3% of total fat in the calorically-dense infant formula*

would be corn oil. However, this assumption is based on common levels of fat in non-exempt infant formulas for term infants.

1) What is the maximum level of fat used in energy-dense exempt infant formulas described in your intended use?

2) Please include a narrative on the safe use of this ingredient if the maximum use level is expected to contribute >50% of total energy, as is the case for current exempt infant formulas on the market.

Response to Question 1b: The maximum level of fat used in energy-dense exempt infant formula will be 50%; the typical range of fat used is 48-50% of the formula. We recognize for current exempt infant formulas on the market, the maximum level of fat can be higher than 50%. However, we hereby clarify the intended use of corn oil under GRN 900 will only be used in energy-dense exempt infant formula with maximum level of fat at 50% of total energy.

- ***FDA Question #1c**: Please explain the basis for limiting corn oil to 3% of the fat blend, and include any technological or nutritional limitations in your narrative.*

Response to Question 1c: Corn oil is limited to 3% of the fat blend to achieve the targeted total fatty acid profile for the targeted infant population described in the intended use. As described in Table 1 of the GRN 900, corn oil is one of the richest commercial oil sources of linoleic acid (LA) and is typically lower in alpha linolenic acid (ALA). The 3% rate of inclusion enables an optimal total fatty acid profile for the target infant population and an optimal omega 6 (LA) / omega 3 (ALA) ratio within the fat blend of the calorically-dense infant formula. There are no technological or nutritional limitations to use corn oil.

- ***FDA Question #1d**: We note that commercially-available, calorically-dense infant formulas contain medium-chain triglycerides and/or vegetable oils. Do the intended uses of corn oil include formulas made with medium-chain triglycerides as the fat source or will corn oil be used as part of a blend of conventional vegetable oils?*

Response to Question 1d: The exempt formula to which the corn oil will be added to contains a blend of fat sources including corn oil, conventional vegetable oils, and other fat sources (e.g., milk fat), including Medium-Chain Triglycerides (MCT) oil. The amount of MCT oil added to the high calorie formula is a level that provides for the most optimal total fatty acid profile for the target infant population.

- ***FDA Question #1e**: Do the intended uses include both milk- and soy-based infant formulas?*

Response to Question 1e: The intended uses only include milk-based infant formulas.

Question #2 Source corn material (Chemistry):

- ***FDA Question #2a****: Please confirm if the corn starting material is Zea mays L. (Fam. Gramineae).*

Response to Question 2a: Yes.

- ***FDA Question #2b****: Please clarify if the corn (grain) source material is grown in the U.S. and is produced in accordance with good agricultural practices (GAPs). If it is not sourced from within the U.S., please clarify that the corn is produced in accordance with GAPs and meets relevant U.S. regulations and guidance for food-grade corn.*

Response to Question 2b: This corn (grain) source material is not produced in the U.S. Instead, it is grown in the European Union (EU) and is produced in accordance with applicable EU requirements and regulations for food-grade corn under GAPs. The corn oil ingredient is further made with the corn grain at a production site that is FSSC 22000 (for food production) certified (certification provided in Appendix A of GRN 900). The corn grain production site is also FSSC 22000 certified and the certification is audited each year by the third-party auditor TÜV Nord Cert. Each supplier is also subject to internal quality evaluation and audits to ensure only food-grade corns are used and the corn oil ingredient is manufactured following cGMP.

- ***FDA Question #2c****: You cite limits for mycotoxins in the corn oil. Please confirm that the corn grain starting material meets limits for mycotoxins established for food-grade corn, including the FDA action level for total aflatoxin and guidance level for fumonisin. (See FDA's Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds2)*

Response to Question 2c: We recognize the importance of monitoring the levels of environmental contaminants such as aflatoxin and fumonisin levels given the corn oil is manufactured from corn. As discussed in Table 9 of GRN 900, the maximum permitted levels of aflatoxin and fumonisin in corn oil are summarized below:

Component	**Maximum Residue Limit**
Aflatoxin B1	0.10 ppb
Aflatoxin B2	0.10 ppb
Aflatoxin G1	0.10 ppb
Aflatoxin G2	0.10 ppb
Sum Aflatoxins B/G	0.10 ppb
Fumonisins (B1 + B2)	200 ppb

We respectfully submit that the specifications for aflatoxins and fumonisin levels provided above are below the FDA action level for total aflatoxin (i.e., 20 ppb for human food) and guidance level for fumonisin (i.e., 2~4 ppm or 2,000~4,000 ppb for various corn products). (See FDA's

Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds) and ensure the intended use of the corn oil ingredient does not present any human safety concern.

Further, as discussed in our response to FDA Question#2b, the starting material corn is grown in the EU and is produced in accordance with applicable requirements for food-grade corns. In particular, under EU Regulation EC No 1881/2006, food-grade corn that is used to produce an ingredient in food stuffs shall not contain 5 ppb aflatoxin B1 or 10 ppb total aflatoxin. Similarly, unprocessed maize shall not contain fumonisins (B1 + B2) at levels exceeding 2 ppm or 2,000 ppb. These EU limits are comparable to the US FDA limits provided in FDA's Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds.

Question #3 Method of Manufacture (Chemistry):

- ***FDA Question #3a****: You list specifications for hexane, acetone, and methanol. Corn oil is generally obtained by solvent extraction, but it is unclear why three solvents are listed. Please clarify how these solvents are used in the method of manufacture.*

Response to Question 3a: Among the three solvents hexane, acetone, and methanol that are tested, only hexane is used in the crude oil extraction process from corn. Specifically, hexane is used to separate the corn oil from the corn germ. The corn oil bounds itself to the hexane. During distillation, the hexane is separated from the corn oil. Any residual hexane is further removed in the refining process (deodorization steps, high temperature).

We do not intentionally use acetone or methanol in the corn oil manufacturing process. As the same manufacturing facility may also process other vegetable oils, we list specifications for acetone and methanol out of an abundance of caution for all potential solvents that might be present in the corn oil as contaminants. Indeed, as described in Appendix C, the test results show all three solvents measured are below detection limit of the analytical method (< 0.5 ppm).

- ***FDA Question #3b****: Please provide a statement that any processing aids, materials, and components added during manufacture are food grade, and safe and suitable for their intended use. For bleaching and filtration materials, please cite the applicable food contact regulation or effective food contact notification for use of those materials.*

Response to Question 3b: Please find a statement attached confirming that all processing aids are food grade, and safe and suitable for their intended use in infant formulas by adhering to relevant European legislations (**Attachment A**). For bleaching and filtration materials including activated carbon, bleaching earth and citric acid that are used as processing aids during the oil refining process are covered by the same statement.

- ***FDA Question #3c****: Activated carbon is listed as optional for removal of polyaromatic hydrocarbons (PAH). What is the source of PAH in the corn oil?*

Response to Question 3c: The source of PAH is from environmental contamination, and PAH is not formed during the manufacturing process. Given the intended use of corn oil in the sensitive infant populations, we closely monitor environmental contaminants including PAH. PAHs are monitored and the maximum levels are noted in Appendix C of GRN 900 under EU regulation EC 1881/2006. Please find an additional statement attached confirming the source of the PAH from the supplier. (**Attachment B**).

- ***FDA Question #3d****: Please provide statements about the ability of the method of manufacture to remove contaminants listed in your batch analyses (i.e., mycotoxins, persistent organic pollutants).*

Response to Question 3d: As described in Figure 2 of GRN 900, contaminants including mycotoxins and persistent organic pollutants are removed during the refining of the corn oil. In particular, bleaching of the neutralized oil removes color pigments, metals, and oxidation

products. The neutralized oil is treated with bleaching earth under vacuum which absorbs the impurities over a set time. In some cases, activated carbon is also used as a processing aid to remove contaminants. Deodorization is the final step of the refining process, which ensures the removal of any possible volatile substances (i.e., taste and odor compounds) as well as contaminants (i.e., pesticide residues and light PAHs). Deodorization is a steam distillation process which is attained by ensuring a high steam temperature in a vacuum over a set time, thus removing volatile substances while retaining vitamins and sterols.

- ***FDA Question #3e****: You have a specified limit for fumonisins on page 17 of the notice, but do not include these mycotoxins in your batch analyses. Please address this discrepancy.*

Response to Question 3e: We apologize for any confusion. We provided the specifications for corn oil in Table 5 following the corn oil monograph of the Food Chemical Codex (FCC) 11 specifications. Batch analysis summarized in Table 6 demonstrates four non-consecutive batches that meet the specifications. On page 17 of the notice, we provided the maximum levels of mycotoxins in corn oil in Table 9 and provided the representative level from one batch. We would like to clarify that unlike the ingredient specifications provided in Table 5, we do not test mycotoxin levels in every batch. Instead, they are tested quarterly as part of an on-going monitoring program.

- ***FDA Question #3f****: You provide limits for glycidyl fatty acid esters as glycidol, but do not address 2- and 3-monochloropropane diols. Please clarify if your refining method incorporates strategies to mitigate formation of these contaminants. For a discussion of mitigation strategies, please refer to the Codex Code of Practice (CoP) 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 3f: We recognize the exposure to 3-MCPDE and GE can occur through consumption of refined oils such as corn oil. In addition to limits for GE, 3-MCPDE level in corn oil is also monitored. Please find attached a monitoring program in place specifically for 3-MCPDE and a limit of 250 ppb (0.25 ppm) in corn oil (**Attachment C**). This limit is established based on risk assessments. In particular, assuming a 90^{th} percentile intake of corn oil at 0.24 g/kg bw/day from the intended use in calorically dense formula and a maximum of 0.25 ppm 3-MCPDE in corn oil, the maximum estimated exposure to 3-MCPDE is 0.06 mcg/kg bw/day. The exposure is well below the limits established by JECFA and the European Food Safety Authority (EFSA).

While the maximum limits for 3-MCPDE and GE ensure the contaminants would not pose any human safety concern, 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.

Question #4 Composition (Chemistry):

- ***FDA Question #4a****: You provide analytical values for Vitamin E and Vitamin K. We note that while you cite USDA Nutrient Database values for vitamins in corn oil, those values are limited and do not encompass the values in your batch analyses. Please provide a narrative, citing appropriate references, to support how your ingredient compares with typical ranges of vitamins in corn oil.*

Response to Question 4a: In GRN 900, we discussed that because corn oil is a source of fat-soluble vitamins, the ingredient would contain naturally-occurring vitamin E and vitamin K. Vitamin E and K are not added during the manufacturing process but as corn oil is a natural product there can be a natural variation in compounds such as vitamins due to growing conditions, weather, region, etc. Vitamins are naturally present in raw materials and as the corn goes through a refining process, can be present in the finished corn oil.

We note that according to USDA Nutrient Database, typical corn oil contains approximately 14.3 mg vitamin E (alpha-tocopherol) per 100 g oil and 1.9 µg vitamin K (phylloquinone) per 100 g oil. As the USDA data are limited, they do not encompass the vitamin E and vitamin K levels reported in the corn oil ingredient under GRN 900, which is reported to contain vitamin E approximately at 45 mg per 100 g oil and the concentration of vitamin K in the range of 12.9 to 20.2 µg per 100 g oil. We believe that our corn oil contains higher levels of vitamin E and vitamin K than USDA reported is either because the refining process helps further remove undesirable contaminants or the natural variation associated with naturally-occurring vitamin levels. Indeed, according to Codex Standard for Named Vegetable Oils (CODEX-STAN 210 - 1999), corn oil is reported to contain 23-573 mg/kg vitamin E, which would encompass our level of 450 mg/kg.

- ***FDA Question #4b****: Phytosterol batch analyses do not include cholesterol or brassicasterol, which are listed in the Codex Named Oils Standard. Further, there are two phytosterols (campestanol and sitostanol) that are quantified in your batch analyses but not included in the Codex reference. Please clarify this apparent discrepancy or provide a narrative that addresses the phytosterol values reported in your batch analyses. Please include appropriate citations in your discussion.*

Response to Question 4b: We apologize for the omission of cholesterol and brassicasterol levels, which were actually measured in the 3 batch analysis included in the dossier. As reported in **Attachment D**, results for cholesterol were 0.2% in all 3 batches. Results for brassiciasterol were 0.7%, 0.2% and 0.3% in the batches.

The campestanol and sitostanol levels in the corn oil were provided in the broader sterol analysis provided in the dossier. As shown in Table 3, these components account for a relatively small percentage of sterols in corn oil. These components also are present in low percentages in other oils used in infant formula such as safflower oil (Salaberría et al., 2016).

- ***FDA Question #4c****: Please confirm the range of values given in the iodine value specification. The lower value of the range falls outside the Food Chemicals Codex limits.*

Response to Question 4c: To be consistent with the Food Chemical Codex, we agree the iodine specification should be modified from the existing 118-128 to 120-130. The batch analysis data in Table 6 of GRN 900 have shown the ingredient complies with the FCC iodine specification.

Question #5 Stability (Chemistry):

- ***FDA Question #5a****: Please address the stability of corn oil in infant formula.*

Response to Question 5a: The stability of corn oil is similar to other common vegetable oils. Corn oil has a minimum shelf life of 6 months if stored below 15°C away from light under nitrogen. When used in the calorically dense formula, any creaming of fat in corn oil is delayed as much as possible by the emulsifier up to the end of shelf life of the final product (i.e., 12 months). The emulsifier facilitates a proper remixing of the oil blend including the corn oil. The fatty acids that are coming from corn oil and from other oils are stable throughout the shelf life of the final infant formula product.

- ***FDA Question #5b****: Please clarify if food-grade antioxidants are added to the oil for stability.*

Response to Question 5b: There are no antioxidants added to the corn oil for stability.

Question #6 Environmental Contaminants (Chemistry):

- ***FDA Question #6a****: Please discuss the environmental contaminants listed in your batch analyses (i.e., dioxins, furans, pesticides, PCBs) in the context of U.S. regulations and guidance where available. Please provide a brief discussion of residual contaminants that may be present in your ingredient.*

Response to Question 6a: According to the Food Chemicals Codex 11th monograph for corn oil, the only environmental contaminants that are listed as part of the ingredient specifications are lead and arsenic. In particular, under the Food Chemicals Codex, arsenic and lead levels in corn oil cannot exceed 0.5 mg/kg and 0.1 mg/kg, respectively. GRN 900 has established heavy metal limits even lower than the Food Chemicals Codex – 0.1 mg/kg for arsenic and 0.01 mg/kg for lead. Importantly, the Food Chemicals Codex does not contain limits for other environmental contaminants. We also do not believe any of other environmental contaminants are expected to be present in the corn oil ingredient. The corn oil supplier has a FSSC 22000 certification, and as discussed in GRN 900 the manufacturing process for corn oil has the ability to remove any potential undesirable compounds.

Given the intended use in infant formula, and out of an abundance of caution, Table 10 of GRN 900 provides the maximum limits of environmental contaminants including dioxin and PCBs, which are copied below. These environmental contaminants are not part of the ingredient specifications, but are tested every quarter through a monitoring program.

Component	**Maximum Residue Limit**	**Unit**
Sum of dioxins (WHO-PCDD/F-TEQ)	0.3	pg/g fat
Sum of dioxins and dioxin-like PCB's (WHO-PCDD/F-PCB-TEQ)	0.5	pg/g fat
Sum of PCB28, PCB52, PCB101, PCB138, PCB153, PCB18	1.0	ng/g fat
Glycidyl fatty acid esters expressed as glycidol	300	mcg/kg
Bens(a)pyrene (BaP)	1.0	mcg/kg
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	2.0	mcg/kg

Under 21 CFR §109.30, temporary tolerance for PCBs in infant and junior foods is 0.2 ppm whereas our maximum residual limit for sum of dioxin and dioxin-like PCBs in corn oil is only 0.5 pg/g or ppt. We respectfully submit that the maximum levels provided in the table above, which are based on international standards, ensure the corn oil ingredient will not contain dioxin or PCB at levels that would pose safety concern for the intended use.

- ***FDA Question #6b****: Please provide a statement that the starting material (corn grain) and/or corn oil meets U.S. regulatory limits and action levels for pesticides. We note that there are tolerances and exemptions for pesticides (40 CFR Part 180) and action levels (listed in CPG 575.100)4 for persistent pesticides in foods, including corn.*

Response to Question 6b: We hereby confirm the corn oil ingredient under GRN 900 meets all applicable U.S. regulatory limits and action levels for pesticides. In Appendix C of GRN 900, the supplier states that organochlorine and organophosphorous pesticides levels would not exceed 0.01 mg/kg or ppm in the corn oil ingredient. The supplier production site is also FSSC 22000 (for food production) certified and the certification is audited each year by the third-party auditor TÜV Nord Cert. Each incoming good is verified food-grade and is reviewed under internal quality evaluations.

- ***FDA Question #6c****: Please provide a statement that the starting material (corn grain) and/or corn oil does not exceed the derived intervention levels for radionuclides as listed in CPG 560.750.5*

Response to Question 6c: We hereby confirm the corn oil ingredient under GRN 900 does not exceed the derived intervention levels for radionuclides as listed in CPG 560.750.5.

Question #7 Dietary Exposure (Chemistry):

- ***FDA Question #7a****: The dietary exposure estimates are based on the "highest achieved formula intake" level of 175 kcal/kg body weight (w)/day (d) from a single published study (Clarke et al., 2007) aiming for intake levels up to 200 kcal/kg bw/d. While 175 kcal/kg bw/d or even 200 kcal/kg bw/d may be useful in describing the upper range of possible dietary intakes, this level does not appear to be a reasonable estimate of the 90th percentile dietary intake. We have seen calculations of pseudo-90th percentile dietary exposures for ingredients added to infant formula based on the assumption that the 90th percentile dietary exposure is approximately 1.2 times the mean; however, your cited value is approximately 1.5-1.7 times the mean. Please address whether the cited level of caloric intake (175 kcal/kg bw/d) is reasonable and/or sustainable in the subpopulations that would consume calorically-dense formula. We further request that you consider your response to part a in your response to part b below.*

Response to Question 7a: 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). While we noted in GRN 900 that 200 kcal/kg bw/day could be the highest use level, we believe 175 kcal/kg bw/day is a more representative conservative estimate for the purpose of a safety assessment. As the agency noted, even 175 kcal/kg bw/day may be achieved only 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 dosage 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 #7b****: Please provide estimates of the mean and 90th percentile dietary exposures for infants less than 6 months of age, and for older infants 6-12 months of age consuming this ingredient. Please base your estimates on reference data for caloric needs of the subpopulation(s) of infants consuming energy-dense formulas. You may base caloric needs on published estimates of energy needs for catch-up growth or use other reference data to support your discussion.*

Response to Question 7b: 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 (Schofield 1985). 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 1. 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 2. 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 corn oil, we calculated the estimated daily intake of corn oil and phytosterols below:

Table 3. Estimated Daily Intake of Corn Oil and Phytosterols from the Maximum Proposed Use of Corn Oil

Calorically Dense Formula Intake		Total Fat Intake	Corn Oil Intake	Phytosterol Intake from Corn Oil
Population and intake	kcal/kg bw/day	g/kg bw/day	g/kg bw/day	mg/kg bw/day
Infants 0-6 months				
Typical	120	6.7	0.20	1.6
Pseudo-90th percentile	144	8.0	0.24	1.9

Infants 6-12 months				
Typical	110	6.1	0.18	1.4
Pseudo-90th percentile	132	7.3	0.22	1.7

Assumptions: 100 kcal per 100 mL; fat accounts for 50% of kcal, and 9 kcal per gram of fat; maximum use of 3.0% corn oil in fat blend; average total phytosterol concentration of 777 mg per 100 g oil

Question #8 (Toxicology):

Please address the following gaps in the literature search performed for this notice.

- ***FDA Question #8a**: On page 29 of the notice, the last search associated with corn oil exposure in infants or in infant formula was in March 2019. Please confirm that no relevant references on corn oil exposure in infants or from infant formula were published from March 2019 to just prior to your GRAS notice submission that was dated November 7, 2019, or include details of any supplemental literature searches that were performed.*

Response to Question 8a: An updated literature search was conducted on May 15, 2020, to identify relevant studies that included corn oil in infant formula. The search terms included (infant OR newborn OR formula) AND ("corn oil" OR "maize oil") with limits for human studies, papers in the English language, and publication from 2019-2020. Three papers (listed below) were identified in the search update, none of which were relevant for this safety assessment.

Kerling EH, Hilton JM, Thodosoff JM, Wick J, Colombo J, Carlson SE. Effect of Prenatal Docosahexaenoic Acid Supplementation on Blood Pressure in Children With Overweight Condition or Obesity: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2019 Feb 1;2(2):e190088. doi: 10.1001/jamanetworkopen.2019.0088.

Schoener AL, Zhang R, Lv S, Weiss J, McClements DJ. Fabrication of plant-based vitamin D(3)-fortified nanoemulsions: influence of carrier oil type on vitamin bioaccessibility. Food Funct. 2019 Apr 1;10(4):1826-1835. doi: 10.1039/c9fo00116f. Epub 2019 Mar 15.

Soldo D, Mikulić-Kajić M, Spalldi Barišić L, Penava N, Orlović M, Soldo N, Kajić M. Effect of n-3 long-chain polyunsaturated fatty acids supplementation in healthy mothers on DHA and EPA profiles in maternal and umbilical blood: a randomized controlled trial. J Perinat Med. 2019 Feb 25;47(2):200-206. doi: 10.1515/jpm-2018-0155.

- ***FDA Question #8b**: Page 35 of the notice references several searches on the topic of phytosterols (as described on page 51 of Appendix D). The notice states that searches were done to review published literature "since the last safety review in a GRAS notice identified numerous clinical studies of phytosterols." Please indicate which GRAS notice you are referring to in this statement.*

Response to Question 8b: The statement that searches were done to review published literature "since the last safety review in a GRAS notice identified numerous clinical studies of phytosterols" is a reference to GRN 492. The text in GRN 492 states that the most recent searches of the literature referenced in that review were conducted through July 2012 (inclusive). Searches of information on phytosterols in the current GRN notification were conducted from January 2012 to ensure coverage of literature since the time period of the searches covered in GRN 492.

Question #9 (Toxicology):

In Part 6 of the notice (safety narrative) on page 29, the discussion of the absorption, distribution, metabolism, and excretion (ADME) properties of corn oil-containing infant formula is incomplete.

- ***FDA Question #9a**: The ADME discussion is missing information on the distribution and excretion of the digested fatty acid constituents of corn oil. Please briefly describe these two aspects of the ADME of corn oil in infants.*

Response to Question 9a: We apologize for the omission and below, we briefly discuss the distribution and excretion of the digested fatty acid constituents of corn oil. In infants, triglyceride digestion products cross the apical membranes of the enterocytes and are reassembled into triglycerides that are subsequently packaged into chylomicrons (Innis, 2011). The chylomicrons are released into the circulation and are distributed to tissues such as the liver to be metabolized (Manson and Weaver, 1997). Chylomicron triglycerides distributed within the adipose tissue are hydrolyzed and subsequently re-esterified into triglycerides and stored until energy from fat is required, particularly during the postabsorptive state or during exercise (IOM, 2005). Triglycerides that are taken up by muscle are utilized for energy or released into the circulation and are distributed to the liver (IOM, 2005). In general, fatty acid catabolism results in the excretion of carbon dioxide and water (IOM, 2005). Minimal amounts of ketone bodies produced by fatty acid oxidation are excreted in the urine (IOM, 2005). Additionally, fatty acids in skin and intestinal cells are removed from sloughed cells (IOM, 2005). Excretion of dietary fat via the feces is known to occur during the neonatal stage and in cases of prematurity due to a lack of sufficient fat absorption from the intestines (Rings et al., 2002). A healthy full-term infant has a functional digestive system at birth (reviewed in Zou et al., 2016) and therefore would be expected to have less fecal fat excretion.

- ***FDA Question #9b**: Phytosterols are a significant component of corn oil compared to other oils. Please provide a description of the ADME properties of phytosterols in infants.*

Response to Question 9b: Below, we provide a description of the ADME properties of phytosterols in infants. Understanding of the ADME properties of phytosterols is based largely on studies in adults. In adults, dietary phytosterol bioavailability is low, with absorption being <5% of the dietary load as demonstrated in multiple studies (Ostlund et al., 2002; Heinemann et al., 1993; EFSA 2012). While data are available on the absorption of phytosterols, the distribution of phytosterols in humans remains to be elucidated. Absorbed phytosterols are subsequently transported in the serum via LDLs to organs and tissues including the liver (Ling and Jones, 1995; Moghadashian, 2000; Sanders et al., 2000; Hamada et al., 2006; Scolaro et al., 2019). In the liver, phytosterols are converted to bile acids and are excreted via the biliary route into the feces (Ling and Jones, 1995; 1995; Moghadashian et al., 2000; Sanders et al., 2000; Hamada et al., 2006; Scolaro et al., 2019). Phytosterols not absorbed in the gastrointestinal tract enter the colon intact and are eliminated in the feces (Ling and Jones, 1995).

Information regarding the ADME of phytosterols in infants is limited. Hamdan et al. (2018) showed in an in vitro digestion study that the bioaccessibility of total sterols from infant formula was 76% in formula containing only vegetable oils and 72% in formula containing vegetable oils, milk fat, and milk fat globule membranes, with lower bioaccessibility of plants sterols compared to cholesterol. Babawale et al. (2018) determined that phytosterols in formula may inhibit cholesterol absorption and enhance cholesterol synthesis. Studies conducted in infants suggest that phytosterol absorption decreases with age, as infants were shown to have higher phytosterol absorption than children, while both cohorts have been shown to have higher absorption than adults (Salen et al., 1970; Mellies et al., 1976; Nghiem et al., 2015; Scolaro et al., 2019). Separately, Tammi et al. (2001) determined that phytosterol absorption in children was comparable to absorption observed in adults.

Question #10 (Toxicology):

- ***FDA Question #10****: The studies described in the notice in the exposure and safety evaluations employed different infant feeding methods. The published studies on pages 20-21 used to derive estimates of exempt infant formula intake levels involved enteral feeding. However, most of the published studies discussed on pages 29-37 involved oral formula consumption. Please briefly address how the use of studies involving standard oral infant formula intake are relevant to the safety evaluation of enteral infant formula intake. Additionally, please compare the caloric or energy intake (e.g., amount, average, range) reported for these two different feeding study groups (enteral vs. oral).*

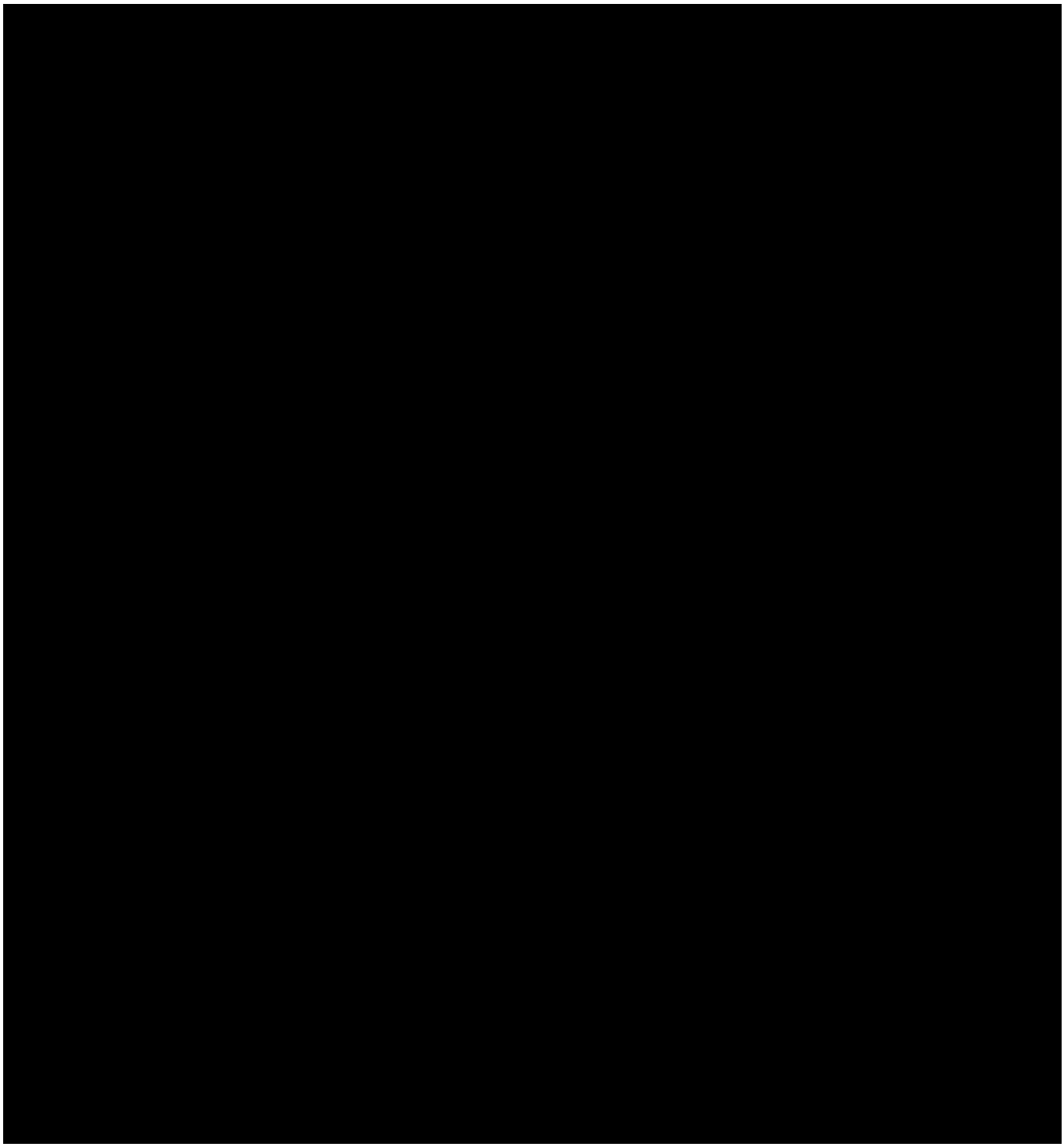
Response to Question 10: We respectfully submit that in terms of dietary exposure assessment and safety evaluations for the purpose of GRN 900, there is no difference between enteral feeding and standard oral consumption. Enteral nutrition is nutrition provided through the gastrointestinal tract via a tube, catheter, or stoma and thus delivers nutrients distal to the oral cavity (Bankhead et al., 2009). Nutrition provided by mouth also uses the same gastrointestinal tract and is therefore a form of enteral nutrition. For pediatric patients who may be unable to feed through oral ingestion, enteral nutrition via a tube or catheter is the recommended route of delivery as enteral feedings are recognized to be beneficial for maintaining gastrointestinal mucosal integrity and motility (Mehta et al., 2017). Parental nutrition, or intravenous feeding, is the route of delivery only when enteral nutrition is not feasible. Infant formulas developed for oral feeding or tube feeding have the same nutrient composition as the specific route of delivery via the gastrointestinal tract (i.e., orally or via a tube, catheter, or stoma) does not impact nutrient needs. As such, the difference in how infants consume the exempt formula with corn oil added does not impact the safety evaluation or dietary exposure assessment for these two different feeding study groups (enteral vs. oral).

The referenced studies of infants consuming calorically dense infant formula describe infant populations of representative of some of the target populations for the calorically dense infant formula to which corn oil is proposed for use. The infants in these trials are patients in pediatric wards for medical conditions including respiratory failure due to viral bronchiolitis, congenital heart disease, chronic lung disease, non-organic failure to thrive, or other conditions typically requiring enteral administration via a tube or catheter, and infants with faltering growth due to cardiac lesions, cystic fibrosis, or other causes that may be able feed orally.

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). As summarized in Table 3 below and reviewed above in Question 7, the nutrient needs of infants in these trials were reported to have been identified by application of a predictive equation or the stated goals were consistent with values from predictive equations, not based on the feeding method (enteral vs. oral).

The energy intake reported for infants in the referenced trials containing corn oil in infant formula are provided in Table 3 below (Ponder et al., 1992; De Souza et al., 2017; Leite et al., 2013; Hayes et al., 1992). The energy intake by these healthy term infants ranged from

approximately 95 to 101-125 kcal/kg bw/day, which is consistent with the energy requirements for healthy infants as identified by the IOM (2005). The healthy term infant populations in these studies consumed these formulas by mouth. Given that the formulas were provided via an enteral route, it is appropriate to compare intakes on a body weight basis between this population and the target population. Such comparisons are made for the safety assessment as presented in Questions 10 and 11 below. Please note the table below provides a comparison of the caloric or energy intake (e.g., amount, average, range) reported for these two different feeding study groups (enteral vs. oral). As noted, the energy intakes, reported for these two different feeding study groups (enteral vs. oral) are different. However, the difference is a function of the infant populations, not the route of delivery.



Questions #11&12 (Toxicology): (We combine our response to questions 11 and 12 below).

- ***FDA Questions #11&12****:*

  #11 *In the section titled "Clinical Studies of Infants Consuming Corn Oil" beginning on page 29 of the notice, you described the findings of published studies that examined the effects of corn oil-based infant formula in infants, and exposure to complementary food products containing corn oil. However, a safety assessment that employs these findings was not performed. A comparison between the level of exposure to corn oil (or its constituents) in infants from consumption of the proposed exempt infant formula and the exposure to corn oil (or its constituents) in infants found at effect levels in the described published studies is needed to evaluate the safety of the proposed infant formula exposure. Please discuss this safety evaluation as part of your safety narrative.*

  #12 *In the section titled "Phytosterols in the Infant Diet" beginning on page 33 of the notice, you described the findings of published studies and other sources that examined the effects of exposure to phytosterols in food. However, a safety assessment that employs these findings was not performed.*

  A comparison between the level of exposure to phytosterols in infants from consumption of the proposed exempt infant formula and the exposure to phytosterols found at effect levels in the described published studies or sources is needed to evaluate the safety of the proposed infant formula exposure. Please discuss this safety evaluation as part of your safety narrative.

Response to Questions 11&12: As requested by the agency, we now calculate comparisons between the level of exposure to corn oil (or its constituents) in infants from consumption of the proposed exempt infant formula and the exposure to corn oil (or its constituents) in infants found at effect levels in the described published studies to evaluate the safety of the proposed infant formula exposure. For each clinical study referenced in the safety narrative with a quantified amount of corn oil in the formula, the estimated intake of corn oi by infants is calculated below. Based on this estimated intake, the amount of phytosterol provided by the formula is also calculated assuming a concentration of mean phytosterol in corn oil based on analytical data (777 mg per 100 g oil). We present these calculations to compare the specific exposures to corn oil in these studies with the proposed exposure to corn oil (and its constituent, phytosterol) from the intended use in calorically dense formula. In GRN 900 we note that published studies in which corn oil is a component of the fat blend (up to 50%) provide evidence on the suitability of corn oil as a component of the fat blend in infant formula.

As presented on page 22 of the GRAS notification, the estimated intake of corn oil for its intended use is 0.2 g/ kg bw/day at the mean assuming energy intake of 120 kcal/kg bw/day. As detailed above in Question 7, the pseudo-90th percentile intake of 144 kcal/kg bw/day may be more representative of anticipated "high" consumption of the calorically dense formula. Based on these estimates of mean and pseudo-90th percentile formula intake, exposure to corn oil (assuming a maximum of 50% of energy from fat in the formula, and 3% of fat as corn oil),

the mean and pseudo-90th percentile exposure to corn oil are calculated to be 0.20 and 0.24 g/kg bw/day, respectively.

The estimated intake of corn oil from clinical trials among healthy infants that provided the concentration of corn oil in formula or complementary foods is summarized in the Table 4 below. The estimated intake of corn oil by healthy infants consuming corn oil as a component of the fat blend in infant formula ranges from 2.0 to 3.4 g/kg bw/day. In trials that provided corn oil in complementary foods, the estimated corn oil intake ranged from 0.5 to 0.9 g/kg bw/day. The estimated intake of corn oil for its intended use is lower than levels consumed in other clinical trials among healthy infants.

The estimated intake phytosterols from corn oil for its intended use is 1.6 mg/kg bw/day and the mean and 1.9 mg/kg bw/day at the pseudo-90th percentile. The estimated intake of phytosterols from corn oil in clinical trials among infants and children that provided corn oil in formula or complementary foods is summarized in the Table 4 below. The estimated intake of phytosterols from infant formula ranges from 15.5 to 58.8 mg/kg bw/day. In trials that provided corn oil in complementary foods, the estimated corn oil intake ranged from 6.0 to 211 mg/kg bw/day. The estimated intake of phytosterols from corn oil for its intended use is lower than levels consumed in other clinical trials among healthy infants and the JECFA ADI of 40 mg/kg bw/day.

Table 5. Estimated Corn Oil and Phytosterol Intake in Clinical Trials among Healthy Infants

Study	Study Population; Age at Baseline	Corn Oil/Phytosterol Exposure; Intake Duration	Estimated Corn Oil Intake (g/kg bw/day)	Estimated Phytosterol Intake (mg/kg bw/day)	Assumptions*
Exposures from Infant Formula					
Ponder et al., 1992	14 Healthy, full-term infants; 0 - 3 d	infant formula containing 1.8 g corn oil/100 mL; 8 wk	2.75 - 3.4	21.4 - 26.4	Energy density: 67 kcal/100 mL. 3.65 g fat per 100 mL, 50% fat from corn oil Energy Intake: 101 - 125 kcal/day Body Weight: 5.15 kg Phytosterols: 777 mg/100 g corn oil (average of analytical data)
De Souza et al., 2017; Leite et al., 2013	16 Healthy, full-term infants; 108 ± 27 d	infant formula containing 1.4 g corn oil/100 mL; 14 d	2.0	15.5	Energy density: 67 kcal/100 mL Energy intake: 95 kcal/kg (IOM) Body Weight: 6.0 kg (IOM) Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Hayes et al., 1992	15 Healthy, full-term infants; 0 d	infant formula containing 3.1 g corn oil per 100 kcal and 35% kcal from fat, 4 mo	3.4	26.7	Energy as fat: 79.5% fat as corn oil (3.1 g out of of 3.9 g per 100 kcal) Energy Intake: 535 kcal/day Body Weight: 4.8 kg [average of initial (3.509 kg) and final BW (6.123 kg)] Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Mellies et al., 1976	53 Healthy infants or infants with familial hypercholesterolemia; 2 mo	24 oz infant formula containing 26.8 g vegetable oil and 300 mg phytosterols; cross-sectional	-	58.8	Energy Intake: 482 kcal/day Body Weight: 5.1 kg [average of male/female birth - 2 mo (CDC)]
Mellies et al., 1976	53 Healthy infants or infants with familial hypercholesterolemia; 8.5 mo	32 oz infant formula containing 39.0 g vegetable oil and 400 mg phytosterols; cross-sectional	-	48.5	Energy Intake: 1,065 kcal/day Body Weight: 8.25 kg [average of male/female 6 - 8 mo (CDC)]
Exposures from Complementary Foods					
Schwartz et al., 2009	53 Healthy, full-term infants; 4 mo	complementary food containing 3.4 g corn oil; 6 mo	0.5	3.8	Body Weight: 7 kg Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Libuda et al., 2016	72 Healthy, full-term infants; 4 - 6 mo	complementary food containing 2.66 or 3.08 g	0.8 or 0.9	6.0-6.9	Food intake: 190 or 220 g Body Weight: 3.46 kg Phytosterols: 777 mg/100 g

		corn oil; 4 - 6 mo			corn oil (average of analytical data)
Tammi et al., 2001	40 Healthy children; 13 mo	low saturated fat & cholesterol diet + vegetable oil or margarine containing 132 mg phytosterols; 1 mo	-	13.1	Body Weight: 10.1 kg
Garoufi et al., 2014	64 Children, 30 with hypercholesterolemia and 34 healthy; 9 mo (range 4.5 - 16)	complementary food containing 2 g phytosterols; 6-12 mo	-	211	Body Weight: 9.5 kg [average of male/female 9-11 mo (CDC)]

% of fat blend from corn oil not reported in Goalwin and Pomeranze, 1962; Uauy et al., 1990; Uauy et al., 1994; Hoffman et al., 1999; Schouten, 2013.

*Values as reported in manuscript or based on assumed values.

Question #13 (Toxicology):

- ***FDA Question #13****: In your amendment from May 1, 2020, which 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)." 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 corn oil ingredient in a calorically-dense formula (i.e., expected to provide more fat per feeding) considering the gastrointestinal abnormalities often found in infants with CF (e.g., Wouthuyzen-Bakker et al., 2011).*

Response to Question 13: 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). 1/ For infants with CF who demonstrate weight loss or inadequate weight gain, calorie-dense feedings are recommended. 2/

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 – 67 kcal/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 when to the current practice.

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 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 calorically density of feedings is

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1/ 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.

2/ *See id*.

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

Question #14 (Final Formatting):

- ***FDA Question #14****: Please state your conclusion that your intended use of corn oil is GRAS based on the totality of data and information provided in your GRAS notice.*

Response to Question 14: In conclusion, the intended use of corn oil is GRAS based on the totality of data and information provided in the GRAS notice.

Question #15:

- ***FDA Question #15****: The numbering of the tables in the GRAS notice is inaccurate. For example, on page 4 of the notice in the "List of Tables," eleven tables and their titles are listed. However, thirteen tables are presented in the text of the notice. Beginning with Table 9, the table listing is inaccurate, as are some of the references to specific tables in the text of the notice. Please clarify the table listings and provide statements correcting the table references. A revised copy of the affected pages is not necessary.*

Response to Question 15: We apologize for the discrepancy and confusion. Copied below is the correct table reference.

Page	Correction
19	The reference to Table 9 on this page should instead reference Table 11 (which appears on page 20).
20	The table title should be Table 11. Formula Intake in Studies of Term Infants Consuming a Calorically Dense Infant Formula
22	The two references to Table 10 on this page should instead reference Table 12 (which appears on page 22).
22	The table title should be Table 12. Estimated Daily Intake of Corn Oil and Phytosterols from the Maximum Proposed Use of Corn Oil
25	The three references to Table 11 on this page should instead reference Table 13 (which appears on page 26).
26	The table title should be Table 13. Fat and Fatty Acid Requirements in Infant Formula for Term Infants
39	The reference to Table 10 on this page should instead reference Table 12 (which appears on page 22).

* * *

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

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[redacted]

20-05-2020

To whom it may concern

Statement regarding Corn oil [redacted] (Material: 6280)

We hereby confirm that all processing aids and materials which are in contact with this product at [redacted] are food grade and our suppliers adhere to the relevant European legislation. This is supplied [redacted] for infant nutrition use and thus Corn oil (material 6280) complies to [redacted] statement concerning contaminants for oils and fats for infant nutrition.

[redacted] has been assessed and determined to comply with the requirements of FOOD SAFETY SYSTEM CERTIFICATION 22000, please see latest sign certificate for more information.

[redacted]

[redacted]

[redacted]

05-06-2020

To whom it may concern

Statement regarding Corn oil [redacted] (Material: 6280)

With reference to above-mentioned product, Benzopyrenes (BaP) and polycyclic aromatic hydrocarbons (PAHs) comply with the maximum limit permitted for vegetable oils for food and infant formula according to EU legislation EC 1881/2006.

Benzopyrenes (BaP) are polycyclic aromatic hydrocarbons (PAHs), a group of chemical compounds that are formed by the incomplete combustion of organic matter. If present in incoming raw materials, they will be reduced / removed during the bleaching step of the refining process. These compounds are not intentionally introduced or formed during the manufacturing process of corn oil.

Benzopyrenes (BaP) are polycyclic aromatic hydrocarbons (PAHs) are measured as part of [redacted]'s contaminants monitoring programme for oils and fats for infant nutrition, with maximum limits of 1.0µg/kg and 2.0µg/kg respectively.

[redacted].

[redacted]

[redacted]

19-05-2020

To whom it may concern

Statement regarding 3-MCPD in Corn oil [redacted]

For several years, [redacted] has a monitoring program in place specifically for 3-MCPD of our raw materials and end products. The 3-MCPD analysis is performed by a certified external laboratory.

The 3-MCPD guarantee for Corn oil is given in the table below:

Product	Product number	Sum free 3-MCPD, 3-MCPDester, det. as free 3-MCPD (ppm)
Corn oil	6280	Max 0.25

The *AOCS Cd 29b-13 GC/MS* an accredited method suitable for the analysis of vegetable fats and oils and has a limit of quantification (LOQ) of 0.1mg/kg. Commitments made by [redacted] on specific vegetable oil blends are subject to the limitations of the current validated analytical method capabilities. [redacted] continues with optimization to have 3-MCPD levels as low as possible.

[redacted]

[redacted]

[redacted]

Sterol composition of Corn oil (628000)			
Batch no:	2017017	2023678	2028874
Lot no:	2192057	2201158	2209780
Lot date:	2018-12-14	2018-01-03	2018-01-18
Total Sterols	800 mg/100g	750 mg/100g	780 mg/100g
Campesterol	20.6 %	20.3 %	20.4 %
Campestanol	0.9 %	0.7 %	0.9 %
Stigmasterol	6.7 %	7.3 %	6.9 %
Sitostanol	2.6 %	2.1 %	2.4 %
Beta-sitosterol	62.5 %	64.4 %	64.0 %
Delta5-avenasterol	2.0 %	2.8 %	2.7 %
Delta7-stigmasterol	0.3 %	0.1 %	0.2 %
Delta7-avenasterol	1.5 %	1.2 %	1.2 %
Cholesterol	0.2%	0.2%	0.2%
Brassiciasterol	0.7%	0.2%	0.3%

03-06-2020

[redacted]

[redacted]

From:	Tao, Xin
To:	Morissette, Rachel
Cc:	Steinborn, Steven B.
Subject:	RE: additional questions for GRN 000900 - corn oil
Date:	Monday, June 15, 2020 11:25:13 AM
Attachments:	image001.png Response to FDA"s Additional Questions on GRN 900 (Corn Oil).pdf Attachment B.PDF Attachment C.PDF Attachment D.PDF Attachment A.PDF

Dear Rachel,

Thank you for your note and the options. Attached, please find an updated version with confidential markings and redactions removed in Table 4 of the response. We continue to request part of the information in Attachments A-D are treated as confidential information.

Please let us know if you have any further questions.

Best regards,
Steve and Xin

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Friday, June 12, 2020 12:34 PM
To: Tao, Xin
Cc: Steinborn, Steven B.
Subject: RE: additional questions for GRN 000900 - corn oil

Dear Steve and Xin,

Thank you for sending the responses to our questions. We note that you included confidential information in your responses. While we don't have an issue with Attachments A-D that only redacted the supplier information, we do have an issue with redacted Table 4 as part of the response to Question 10. As I'm sure you are aware, data and information pertaining to safety cannot be kept confidential in a GRAS notice. Therefore, there are two options you might consider.

1. Remove the confidential markings and redactions in Table 4 in response to Question 10 and resubmit a clean version of that document.
2. Remove reference to the unpublished, confidential study and just frame the response using information that's publicly available and resubmit a clean version of the response document.

Either way, we can't move forward with the current version of the response document with confidential markings and redactions.

Please advise how you would like to proceed.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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

From: Tao, Xin <xin.tao@hoganlovells.com>
Sent: Thursday, June 11, 2020 6:03 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Subject: RE: additional questions for GRN 000900 - corn oil

Dear Rachel,

Hope you keep doing well. Attached, please find our response to the agency's additional questions for GRN 000900. Please note that our response and attachments contain confidential commercial and trade secret information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. In accordance with FDA's implementing regulations, if a request for disclosure is received, we would like to ask that we be notified and provided an opportunity to address why the information or materials should not be released.

We would like to thank you again for the flexibility on the timeline. We trust our response addresses all the questions raised by the agency. 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.

Best regards,
Steve and Xin

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From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Wednesday, May 13, 2020 11:26 AM
To: Steinborn, Steven B.
Cc: Tao, Xin
Subject: additional questions for GRN 000900 - corn oil

Dear Mr. Steinborn,

Please see attached our additional questions for GRN 000900 based on your response to our overarching subpopulation question from May 1, 2020. Please let me know if you have any questions at this time. We request a response within 10 business days.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

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Via Electronic Mail

June 15, 2020

Rachel Morissette, Ph.D.
Regulatory Review Scientist
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 FDA's Questions for GRN 000900

Dear Dr. Morissette,

We hereby submit our responses to FDA's questions for GRN 000900, which covers the intended use of corn oil as a source of fat 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 Intended Use (Chemistry):

- ***FDA Question #1a****: Calorically-dense or energy dense formulas are not defined in the notice or in FDA's regulations.*

  1) For the purpose of the notice, does this term refer to infant formulas with 24 kcal per oz (81 kcal/100 mL) and above or are they specifically 100 kcal/100mL?

  2) Please clarify the range of energy densities for infant formulas that meet your definition of calorically-dense infant formulas.

Response to Question 1a: We hereby clarify that for purposes of GRAS Notice 000900 (GRN 900), the term "calorically-dense or energy dense formulas" refers specifically to formulas that provide 100 kcal/100mL. In other words, calorically-dense or energy dense formulas that target energy densities other than 100 kcal/100mL are not the subjects of this notification.

- ***FDA Question #1b****: In your dietary exposure estimate, you note that fat is typically 50% of energy in infant formula and that 3% of total fat in the calorically-dense infant formula*

would be corn oil. However, this assumption is based on common levels of fat in non-exempt infant formulas for term infants.

1) What is the maximum level of fat used in energy-dense exempt infant formulas described in your intended use?

2) Please include a narrative on the safe use of this ingredient if the maximum use level is expected to contribute >50% of total energy, as is the case for current exempt infant formulas on the market.

Response to Question 1b: The maximum level of fat used in energy-dense exempt infant formula will be 50%; the typical range of fat used is 48-50% of the formula. We recognize for current exempt infant formulas on the market, the maximum level of fat can be higher than 50%. However, we hereby clarify the intended use of corn oil under GRN 900 will only be used in energy-dense exempt infant formula with maximum level of fat at 50% of total energy.

- ***FDA Question #1c**: Please explain the basis for limiting corn oil to 3% of the fat blend, and include any technological or nutritional limitations in your narrative.*

Response to Question 1c: Corn oil is limited to 3% of the fat blend to achieve the targeted total fatty acid profile for the targeted infant population described in the intended use. As described in Table 1 of the GRN 900, corn oil is one of the richest commercial oil sources of linoleic acid (LA) and is typically lower in alpha linolenic acid (ALA). The 3% rate of inclusion enables an optimal total fatty acid profile for the target infant population and an optimal omega 6 (LA) / omega 3 (ALA) ratio within the fat blend of the calorically-dense infant formula. There are no technological or nutritional limitations to use corn oil.

- ***FDA Question #1d**: We note that commercially-available, calorically-dense infant formulas contain medium-chain triglycerides and/or vegetable oils. Do the intended uses of corn oil include formulas made with medium-chain triglycerides as the fat source or will corn oil be used as part of a blend of conventional vegetable oils?*

Response to Question 1d: The exempt formula to which the corn oil will be added to contains a blend of fat sources including corn oil, conventional vegetable oils, and other fat sources (e.g., milk fat), including Medium-Chain Triglycerides (MCT) oil. The amount of MCT oil added to the high calorie formula is a level that provides for the most optimal total fatty acid profile for the target infant population.

- ***FDA Question #1e**: Do the intended uses include both milk- and soy-based infant formulas?*

Response to Question 1e: The intended uses only include milk-based infant formulas.

Question #2 Source corn material (Chemistry):

- ***FDA Question #2a****: Please confirm if the corn starting material is Zea mays L. (Fam. Gramineae).*

Response to Question 2a: Yes.

- ***FDA Question #2b****: Please clarify if the corn (grain) source material is grown in the U.S. and is produced in accordance with good agricultural practices (GAPs). If it is not sourced from within the U.S., please clarify that the corn is produced in accordance with GAPs and meets relevant U.S. regulations and guidance for food-grade corn.*

Response to Question 2b: This corn (grain) source material is not produced in the U.S. Instead, it is grown in the European Union (EU) and is produced in accordance with applicable EU requirements and regulations for food-grade corn under GAPs. The corn oil ingredient is further made with the corn grain at a production site that is FSSC 22000 (for food production) certified (certification provided in Appendix A of GRN 900). The corn grain production site is also FSSC 22000 certified and the certification is audited each year by the third-party auditor TÜV Nord Cert. Each supplier is also subject to internal quality evaluation and audits to ensure only food-grade corns are used and the corn oil ingredient is manufactured following cGMP.

- ***FDA Question #2c****: You cite limits for mycotoxins in the corn oil. Please confirm that the corn grain starting material meets limits for mycotoxins established for food-grade corn, including the FDA action level for total aflatoxin and guidance level for fumonisin. (See FDA's Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds2)*

Response to Question 2c: We recognize the importance of monitoring the levels of environmental contaminants such as aflatoxin and fumonisin levels given the corn oil is manufactured from corn. As discussed in Table 9 of GRN 900, the maximum permitted levels of aflatoxin and fumonisin in corn oil are summarized below:

Component	**Maximum Residue Limit**
Aflatoxin B1	0.10 ppb
Aflatoxin B2	0.10 ppb
Aflatoxin G1	0.10 ppb
Aflatoxin G2	0.10 ppb
Sum Aflatoxins B/G	0.10 ppb
Fumonisins (B1 + B2)	200 ppb

We respectfully submit that the specifications for aflatoxins and fumonisin levels provided above are below the FDA action level for total aflatoxin (i.e., 20 ppb for human food) and guidance level for fumonisin (i.e., 2~4 ppm or 2,000~4,000 ppb for various corn products). (See FDA's Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry:

Fumonisin Levels in Human Foods and Animal Feeds) and ensure the intended use of the corn oil ingredient does not present any human safety concern.

Further, as discussed in our response to FDA Question#2b, the starting material corn is grown in the EU and is produced in accordance with applicable requirements for food-grade corns. In particular, under EU Regulation EC No 1881/2006, food-grade corn that is used to produce an ingredient in food stuffs shall not contain 5 ppb aflatoxin B1 or 10 ppb total aflatoxin. Similarly, unprocessed maize shall not contain fumonisins (B1 + B2) at levels exceeding 2 ppm or 2,000 ppb. These EU limits are comparable to the US FDA limits provided in FDA's Compliance Policy Guidance (CPG) Section 555.4001 and FDA's Guidance for Industry: Fumonisin Levels in Human Foods and Animal Feeds.

Question #3 Method of Manufacture (Chemistry):

- ***FDA Question #3a****: You list specifications for hexane, acetone, and methanol. Corn oil is generally obtained by solvent extraction, but it is unclear why three solvents are listed. Please clarify how these solvents are used in the method of manufacture.*

Response to Question 3a: Among the three solvents hexane, acetone, and methanol that are tested, only hexane is used in the crude oil extraction process from corn. Specifically, hexane is used to separate the corn oil from the corn germ. The corn oil bounds itself to the hexane. During distillation, the hexane is separated from the corn oil. Any residual hexane is further removed in the refining process (deodorization steps, high temperature).

We do not intentionally use acetone or methanol in the corn oil manufacturing process. As the same manufacturing facility may also process other vegetable oils, we list specifications for acetone and methanol out of an abundance of caution for all potential solvents that might be present in the corn oil as contaminants. Indeed, as described in Appendix C, the test results show all three solvents measured are below detection limit of the analytical method (< 0.5 ppm).

- ***FDA Question #3b****: Please provide a statement that any processing aids, materials, and components added during manufacture are food grade, and safe and suitable for their intended use. For bleaching and filtration materials, please cite the applicable food contact regulation or effective food contact notification for use of those materials.*

Response to Question 3b: Please find a statement attached confirming that all processing aids are food grade, and safe and suitable for their intended use in infant formulas by adhering to relevant European legislations (**Attachment A**). For bleaching and filtration materials including activated carbon, bleaching earth and citric acid that are used as processing aids during the oil refining process are covered by the same statement.

- ***FDA Question #3c****: Activated carbon is listed as optional for removal of polyaromatic hydrocarbons (PAH). What is the source of PAH in the corn oil?*

Response to Question 3c: The source of PAH is from environmental contamination, and PAH is not formed during the manufacturing process. Given the intended use of corn oil in the sensitive infant populations, we closely monitor environmental contaminants including PAH. PAHs are monitored and the maximum levels are noted in Appendix C of GRN 900 under EU regulation EC 1881/2006. Please find an additional statement attached confirming the source of the PAH from the supplier. (**Attachment B**).

- ***FDA Question #3d****: Please provide statements about the ability of the method of manufacture to remove contaminants listed in your batch analyses (i.e., mycotoxins, persistent organic pollutants).*

Response to Question 3d: As described in Figure 2 of GRN 900, contaminants including mycotoxins and persistent organic pollutants are removed during the refining of the corn oil. In particular, bleaching of the neutralized oil removes color pigments, metals, and oxidation

products. The neutralized oil is treated with bleaching earth under vacuum which absorbs the impurities over a set time. In some cases, activated carbon is also used as a processing aid to remove contaminants. Deodorization is the final step of the refining process, which ensures the removal of any possible volatile substances (i.e., taste and odor compounds) as well as contaminants (i.e., pesticide residues and light PAHs). Deodorization is a steam distillation process which is attained by ensuring a high steam temperature in a vacuum over a set time, thus removing volatile substances while retaining vitamins and sterols.

- ***FDA Question #3e****: You have a specified limit for fumonisins on page 17 of the notice, but do not include these mycotoxins in your batch analyses. Please address this discrepancy.*

Response to Question 3e: We apologize for any confusion. We provided the specifications for corn oil in Table 5 following the corn oil monograph of the Food Chemical Codex (FCC) 11 specifications. Batch analysis summarized in Table 6 demonstrates four non-consecutive batches that meet the specifications. On page 17 of the notice, we provided the maximum levels of mycotoxins in corn oil in Table 9 and provided the representative level from one batch. We would like to clarify that unlike the ingredient specifications provided in Table 5, we do not test mycotoxin levels in every batch. Instead, they are tested quarterly as part of an on-going monitoring program.

- ***FDA Question #3f****: You provide limits for glycidyl fatty acid esters as glycidol, but do not address 2- and 3-monochloropropane diols. Please clarify if your refining method incorporates strategies to mitigate formation of these contaminants. For a discussion of mitigation strategies, please refer to the Codex Code of Practice (CoP) 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 3f: We recognize the exposure to 3-MCPDE and GE can occur through consumption of refined oils such as corn oil. In addition to limits for GE, 3-MCPDE level in corn oil is also monitored. Please find attached a monitoring program in place specifically for 3-MCPDE and a limit of 250 ppb (0.25 ppm) in corn oil (**Attachment C**). This limit is established based on risk assessments. In particular, assuming a 90^{th} percentile intake of corn oil at 0.24 g/kg bw/day from the intended use in calorically dense formula and a maximum of 0.25 ppm 3-MCPDE in corn oil, the maximum estimated exposure to 3-MCPDE is 0.06 mcg/kg bw/day. The exposure is well below the limits established by JECFA and the European Food Safety Authority (EFSA).

While the maximum limits for 3-MCPDE and GE ensure the contaminants would not pose any human safety concern, 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.

Question #4 Composition (Chemistry):

- ***FDA Question #4a****: You provide analytical values for Vitamin E and Vitamin K. We note that while you cite USDA Nutrient Database values for vitamins in corn oil, those values are limited and do not encompass the values in your batch analyses. Please provide a narrative, citing appropriate references, to support how your ingredient compares with typical ranges of vitamins in corn oil.*

Response to Question 4a: In GRN 900, we discussed that because corn oil is a source of fat-soluble vitamins, the ingredient would contain naturally-occurring vitamin E and vitamin K. Vitamin E and K are not added during the manufacturing process but as corn oil is a natural product there can be a natural variation in compounds such as vitamins due to growing conditions, weather, region, etc. Vitamins are naturally present in raw materials and as the corn goes through a refining process, can be present in the finished corn oil.

We note that according to USDA Nutrient Database, typical corn oil contains approximately 14.3 mg vitamin E (alpha-tocopherol) per 100 g oil and 1.9 µg vitamin K (phylloquinone) per 100 g oil. As the USDA data are limited, they do not encompass the vitamin E and vitamin K levels reported in the corn oil ingredient under GRN 900, which is reported to contain vitamin E approximately at 45 mg per 100 g oil and the concentration of vitamin K in the range of 12.9 to 20.2 µg per 100 g oil. We believe that our corn oil contains higher levels of vitamin E and vitamin K than USDA reported is either because the refining process helps further remove undesirable contaminants or the natural variation associated with naturally-occurring vitamin levels. Indeed, according to Codex Standard for Named Vegetable Oils (CODEX-STAN 210 - 1999), corn oil is reported to contain 23-573 mg/kg vitamin E, which would encompass our level of 450 mg/kg.

- ***FDA Question #4b****: Phytosterol batch analyses do not include cholesterol or brassicasterol, which are listed in the Codex Named Oils Standard. Further, there are two phytosterols (campestanol and sitostanol) that are quantified in your batch analyses but not included in the Codex reference. Please clarify this apparent discrepancy or provide a narrative that addresses the phytosterol values reported in your batch analyses. Please include appropriate citations in your discussion.*

Response to Question 4b: We apologize for the omission of cholesterol and brassicasterol levels, which were actually measured in the 3 batch analysis included in the dossier. As reported in **Attachment D**, results for cholesterol were 0.2% in all 3 batches. Results for brassiciasterol were 0.7%, 0.2% and 0.3% in the batches.

The campestanol and sitostanol levels in the corn oil were provided in the broader sterol analysis provided in the dossier. As shown in Table 3, these components account for a relatively small percentage of sterols in corn oil. These components also are present in low percentages in other oils used in infant formula such as safflower oil (Salaberría et al., 2016).

- ***FDA Question #4c****: Please confirm the range of values given in the iodine value specification. The lower value of the range falls outside the Food Chemicals Codex limits.*

Response to Question 4c: To be consistent with the Food Chemical Codex, we agree the iodine specification should be modified from the existing 118-128 to 120-130. The batch analysis data in Table 6 of GRN 900 have shown the ingredient complies with the FCC iodine specification.

Question #5 Stability (Chemistry):

- ***FDA Question #5a****: Please address the stability of corn oil in infant formula.*

Response to Question 5a: The stability of corn oil is similar to other common vegetable oils. Corn oil has a minimum shelf life of 6 months if stored below 15°C away from light under nitrogen. When used in the calorically dense formula, any creaming of fat in corn oil is delayed as much as possible by the emulsifier up to the end of shelf life of the final product (i.e., 12 months). The emulsifier facilitates a proper remixing of the oil blend including the corn oil. The fatty acids that are coming from corn oil and from other oils are stable throughout the shelf life of the final infant formula product.

- ***FDA Question #5b****: Please clarify if food-grade antioxidants are added to the oil for stability.*

Response to Question 5b: There are no antioxidants added to the corn oil for stability.

Question #6 Environmental Contaminants (Chemistry):

- ***FDA Question #6a****: Please discuss the environmental contaminants listed in your batch analyses (i.e., dioxins, furans, pesticides, PCBs) in the context of U.S. regulations and guidance where available. Please provide a brief discussion of residual contaminants that may be present in your ingredient.*

Response to Question 6a: According to the Food Chemicals Codex 11th monograph for corn oil, the only environmental contaminants that are listed as part of the ingredient specifications are lead and arsenic. In particular, under the Food Chemicals Codex, arsenic and lead levels in corn oil cannot exceed 0.5 mg/kg and 0.1 mg/kg, respectively. GRN 900 has established heavy metal limits even lower than the Food Chemicals Codex – 0.1 mg/kg for arsenic and 0.01 mg/kg for lead. Importantly, the Food Chemicals Codex does not contain limits for other environmental contaminants. We also do not believe any of other environmental contaminants are expected to be present in the corn oil ingredient. The corn oil supplier has a FSSC 22000 certification, and as discussed in GRN 900 the manufacturing process for corn oil has the ability to remove any potential undesirable compounds.

Given the intended use in infant formula, and out of an abundance of caution, Table 10 of GRN 900 provides the maximum limits of environmental contaminants including dioxin and PCBs, which are copied below. These environmental contaminants are not part of the ingredient specifications, but are tested every quarter through a monitoring program.

Component	**Maximum Residue Limit**	**Unit**
Sum of dioxins (WHO-PCDD/F-TEQ)	0.3	pg/g fat
Sum of dioxins and dioxin-like PCB's (WHO-PCDD/F-PCB-TEQ)	0.5	pg/g fat
Sum of PCB28, PCB52, PCB101, PCB138, PCB153, PCB18	1.0	ng/g fat
Glycidyl fatty acid esters expressed as glycidol	300	mcg/kg
Bens(a)pyrene (BaP)	1.0	mcg/kg
Sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene (PAH 4)	2.0	mcg/kg

Under 21 CFR §109.30, temporary tolerance for PCBs in infant and junior foods is 0.2 ppm whereas our maximum residual limit for sum of dioxin and dioxin-like PCBs in corn oil is only 0.5 pg/g or ppt. We respectfully submit that the maximum levels provided in the table above, which are based on international standards, ensure the corn oil ingredient will not contain dioxin or PCB at levels that would pose safety concern for the intended use.

- ***FDA Question #6b****: Please provide a statement that the starting material (corn grain) and/or corn oil meets U.S. regulatory limits and action levels for pesticides. We note that there are tolerances and exemptions for pesticides (40 CFR Part 180) and action levels (listed in CPG 575.100)4 for persistent pesticides in foods, including corn.*

Response to Question 6b: We hereby confirm the corn oil ingredient under GRN 900 meets all applicable U.S. regulatory limits and action levels for pesticides. In Appendix C of GRN 900, the supplier states that organochlorine and organophosphorous pesticides levels would not exceed 0.01 mg/kg or ppm in the corn oil ingredient. The supplier production site is also FSSC 22000 (for food production) certified and the certification is audited each year by the third-party auditor TÜV Nord Cert. Each incoming good is verified food-grade and is reviewed under internal quality evaluations.

- ***FDA Question #6c****: Please provide a statement that the starting material (corn grain) and/or corn oil does not exceed the derived intervention levels for radionuclides as listed in CPG 560.750.5*

Response to Question 6c: We hereby confirm the corn oil ingredient under GRN 900 does not exceed the derived intervention levels for radionuclides as listed in CPG 560.750.5.

Question #7 Dietary Exposure (Chemistry):

- ***FDA Question #7a****: The dietary exposure estimates are based on the "highest achieved formula intake" level of 175 kcal/kg body weight (w)/day (d) from a single published study (Clarke et al., 2007) aiming for intake levels up to 200 kcal/kg bw/d. While 175 kcal/kg bw/d or even 200 kcal/kg bw/d may be useful in describing the upper range of possible dietary intakes, this level does not appear to be a reasonable estimate of the 90th percentile dietary intake. We have seen calculations of pseudo-90th percentile dietary exposures for ingredients added to infant formula based on the assumption that the 90th percentile dietary exposure is approximately 1.2 times the mean; however, your cited value is approximately 1.5-1.7 times the mean. Please address whether the cited level of caloric intake (175 kcal/kg bw/d) is reasonable and/or sustainable in the subpopulations that would consume calorically-dense formula. We further request that you consider your response to part a in your response to part b below.*

Response to Question 7a: 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). While we noted in GRN 900 that 200 kcal/kg bw/day could be the highest use level, we believe 175 kcal/kg bw/day is a more representative conservative estimate for the purpose of a safety assessment. As the agency noted, even 175 kcal/kg bw/day may be achieved only 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 dosage 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 #7b****: Please provide estimates of the mean and 90th percentile dietary exposures for infants less than 6 months of age, and for older infants 6-12 months of age consuming this ingredient. Please base your estimates on reference data for caloric needs of the subpopulation(s) of infants consuming energy-dense formulas. You may base caloric needs on published estimates of energy needs for catch-up growth or use other reference data to support your discussion.*

Response to Question 7b: 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 (Schofield 1985). 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 1. 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 2. 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 corn oil, we calculated the estimated daily intake of corn oil and phytosterols below:

Table 3. Estimated Daily Intake of Corn Oil and Phytosterols from the Maximum Proposed Use of Corn Oil

Calorically Dense Formula Intake		Total Fat Intake	Corn Oil Intake	Phytosterol Intake from Corn Oil
Population and intake	kcal/kg bw/day	g/kg bw/day	g/kg bw/day	mg/kg bw/day
Infants 0-6 months				
Typical	120	6.7	0.20	1.6
Pseudo-90th percentile	144	8.0	0.24	1.9
Infants 6-12 months				

Typical	110	6.1	0.18	1.4
Pseudo-90th percentile	132	7.3	0.22	1.7

Assumptions: 100 kcal per 100 mL; fat accounts for 50% of kcal, and 9 kcal per gram of fat; maximum use of 3.0% corn oil in fat blend; average total phytosterol concentration of 777 mg per 100 g oil

Question #8 (Toxicology):

Please address the following gaps in the literature search performed for this notice.

- ***FDA Question #8a**: On page 29 of the notice, the last search associated with corn oil exposure in infants or in infant formula was in March 2019. Please confirm that no relevant references on corn oil exposure in infants or from infant formula were published from March 2019 to just prior to your GRAS notice submission that was dated November 7, 2019, or include details of any supplemental literature searches that were performed.*

Response to Question 8a: An updated literature search was conducted on May 15, 2020, to identify relevant studies that included corn oil in infant formula. The search terms included (infant OR newborn OR formula) AND ("corn oil" OR "maize oil") with limits for human studies, papers in the English language, and publication from 2019-2020. Three papers (listed below) were identified in the search update, none of which were relevant for this safety assessment.

Kerling EH, Hilton JM, Thodosoff JM, Wick J, Colombo J, Carlson SE. Effect of Prenatal Docosahexaenoic Acid Supplementation on Blood Pressure in Children With Overweight Condition or Obesity: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2019 Feb 1;2(2):e190088. doi: 10.1001/jamanetworkopen.2019.0088.

Schoener AL, Zhang R, Lv S, Weiss J, McClements DJ. Fabrication of plant-based vitamin D(3)-fortified nanoemulsions: influence of carrier oil type on vitamin bioaccessibility. Food Funct. 2019 Apr 1;10(4):1826-1835. doi: 10.1039/c9fo00116f. Epub 2019 Mar 15.

Soldo D, Mikulić-Kajić M, Spalldi Barišić L, Penava N, Orlović M, Soldo N, Kajić M. Effect of n-3 long-chain polyunsaturated fatty acids supplementation in healthy mothers on DHA and EPA profiles in maternal and umbilical blood: a randomized controlled trial. J Perinat Med. 2019 Feb 25;47(2):200-206. doi: 10.1515/jpm-2018-0155.

- ***FDA Question #8b**: Page 35 of the notice references several searches on the topic of phytosterols (as described on page 51 of Appendix D). The notice states that searches were done to review published literature "since the last safety review in a GRAS notice identified numerous clinical studies of phytosterols." Please indicate which GRAS notice you are referring to in this statement.*

Response to Question 8b: The statement that searches were done to review published literature "since the last safety review in a GRAS notice identified numerous clinical studies of phytosterols" is a reference to GRN 492. The text in GRN 492 states that the most recent searches of the literature referenced in that review were conducted through July 2012 (inclusive). Searches of information on phytosterols in the current GRN notification were conducted from January 2012 to ensure coverage of literature since the time period of the searches covered in GRN 492.

Question #9 (Toxicology):

In Part 6 of the notice (safety narrative) on page 29, the discussion of the absorption, distribution, metabolism, and excretion (ADME) properties of corn oil-containing infant formula is incomplete.

- ***FDA Question #9a**: The ADME discussion is missing information on the distribution and excretion of the digested fatty acid constituents of corn oil. Please briefly describe these two aspects of the ADME of corn oil in infants.*

Response to Question 9a: We apologize for the omission and below, we briefly discuss the distribution and excretion of the digested fatty acid constituents of corn oil. In infants, triglyceride digestion products cross the apical membranes of the enterocytes and are reassembled into triglycerides that are subsequently packaged into chylomicrons (Innis, 2011). The chylomicrons are released into the circulation and are distributed to tissues such as the liver to be metabolized (Manson and Weaver, 1997). Chylomicron triglycerides distributed within the adipose tissue are hydrolyzed and subsequently re-esterified into triglycerides and stored until energy from fat is required, particularly during the postabsorptive state or during exercise (IOM, 2005). Triglycerides that are taken up by muscle are utilized for energy or released into the circulation and are distributed to the liver (IOM, 2005). In general, fatty acid catabolism results in the excretion of carbon dioxide and water (IOM, 2005). Minimal amounts of ketone bodies produced by fatty acid oxidation are excreted in the urine (IOM, 2005). Additionally, fatty acids in skin and intestinal cells are removed from sloughed cells (IOM, 2005). Excretion of dietary fat via the feces is known to occur during the neonatal stage and in cases of prematurity due to a lack of sufficient fat absorption from the intestines (Rings et al., 2002). A healthy full-term infant has a functional digestive system at birth (reviewed in Zou et al., 2016) and therefore would be expected to have less fecal fat excretion.

- ***FDA Question #9b**: Phytosterols are a significant component of corn oil compared to other oils. Please provide a description of the ADME properties of phytosterols in infants.*

Response to Question 9b: Below, we provide a description of the ADME properties of phytosterols in infants. Understanding of the ADME properties of phytosterols is based largely on studies in adults. In adults, dietary phytosterol bioavailability is low, with absorption being <5% of the dietary load as demonstrated in multiple studies (Ostlund et al., 2002; Heinemann et al., 1993; EFSA 2012). While data are available on the absorption of phytosterols, the distribution of phytosterols in humans remains to be elucidated. Absorbed phytosterols are subsequently transported in the serum via LDLs to organs and tissues including the liver (Ling and Jones, 1995; Moghadashian, 2000; Sanders et al., 2000; Hamada et al., 2006; Scolaro et al., 2019). In the liver, phytosterols are converted to bile acids and are excreted via the biliary route into the feces (Ling and Jones, 1995; 1995; Moghadashian et al., 2000; Sanders et al., 2000; Hamada et al., 2006; Scolaro et al., 2019). Phytosterols not absorbed in the gastrointestinal tract enter the colon intact and are eliminated in the feces (Ling and Jones, 1995).

Information regarding the ADME of phytosterols in infants is limited. Hamdan et al. (2018) showed in an in vitro digestion study that the bioaccessibility of total sterols from infant formula was 76% in formula containing only vegetable oils and 72% in formula containing vegetable oils, milk fat, and milk fat globule membranes, with lower bioaccessibility of plants sterols compared to cholesterol. Babawale et al. (2018) determined that phytosterols in formula may inhibit cholesterol absorption and enhance cholesterol synthesis. Studies conducted in infants suggest that phytosterol absorption decreases with age, as infants were shown to have higher phytosterol absorption than children, while both cohorts have been shown to have higher absorption than adults (Salen et al., 1970; Mellies et al., 1976; Nghiem et al., 2015; Scolaro et al., 2019). Separately, Tammi et al. (2001) determined that phytosterol absorption in children was comparable to absorption observed in adults.

Question #10 (Toxicology):

- ***FDA Question #10****: The studies described in the notice in the exposure and safety evaluations employed different infant feeding methods. The published studies on pages 20-21 used to derive estimates of exempt infant formula intake levels involved enteral feeding. However, most of the published studies discussed on pages 29-37 involved oral formula consumption. Please briefly address how the use of studies involving standard oral infant formula intake are relevant to the safety evaluation of enteral infant formula intake. Additionally, please compare the caloric or energy intake (e.g., amount, average, range) reported for these two different feeding study groups (enteral vs. oral).*

Response to Question 10: We respectfully submit that in terms of dietary exposure assessment and safety evaluations for the purpose of GRN 900, there is no difference between enteral feeding and standard oral consumption. Enteral nutrition is nutrition provided through the gastrointestinal tract via a tube, catheter, or stoma and thus delivers nutrients distal to the oral cavity (Bankhead et al., 2009). Nutrition provided by mouth also uses the same gastrointestinal tract and is therefore a form of enteral nutrition. For pediatric patients who may be unable to feed through oral ingestion, enteral nutrition via a tube or catheter is the recommended route of delivery as enteral feedings are recognized to be beneficial for maintaining gastrointestinal mucosal integrity and motility (Mehta et al., 2017). Parental nutrition, or intravenous feeding, is the route of delivery only when enteral nutrition is not feasible. Infant formulas developed for oral feeding or tube feeding have the same nutrient composition as the specific route of delivery via the gastrointestinal tract (i.e., orally or via a tube, catheter, or stoma) does not impact nutrient needs. As such, the difference in how infants consume the exempt formula with corn oil added does not impact the safety evaluation or dietary exposure assessment for these two different feeding study groups (enteral vs. oral).

The referenced studies of infants consuming calorically dense infant formula describe infant populations of representative of some of the target populations for the calorically dense infant formula to which corn oil is proposed for use. The infants in these trials are patients in pediatric wards for medical conditions including respiratory failure due to viral bronchiolitis, congenital heart disease, chronic lung disease, non-organic failure to thrive, or other conditions typically requiring enteral administration via a tube or catheter, and infants with faltering growth due to cardiac lesions, cystic fibrosis, or other causes that may be able feed orally.

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). As summarized in Table 3 below and reviewed above in Question 7, the nutrient needs of infants in these trials were reported to have been identified by application of a predictive equation or the stated goals were consistent with values from predictive equations, not based on the feeding method (enteral vs. oral).

The energy intake reported for infants in the referenced trials containing corn oil in infant formula are provided in Table 3 below (Ponder et al., 1992; De Souza et al., 2017; Leite et al., 2013; Hayes et al., 1992). The energy intake by these healthy term infants ranged from

approximately 95 to 101-125 kcal/kg bw/day, which is consistent with the energy requirements for healthy infants as identified by the IOM (2005). The healthy term infant populations in these studies consumed these formulas by mouth. Given that the formulas were provided via an enteral route, it is appropriate to compare intakes on a body weight basis between this population and the target population. Such comparisons are made for the safety assessment as presented in Questions 10 and 11 below. Please note the table below provides a comparison of the caloric or energy intake (e.g., amount, average, range) reported in public literature for these two different feeding study groups (enteral vs. oral). As noted, the energy intakes, reported for these two different feeding study groups (enteral vs. oral) are different. However, the difference is a function of the infant populations, not the route of delivery.

Table 4. Formula Intake in Studies of Term Infants Consuming Calorically Dense Infant Formula vs a Standard 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**
Infants consuming a calorically dense formula (assume enteral administration)				
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)
Eveleens et al., 2019	Retrospective study of infants admitted to a pediatric intensive care unit n = 76; 30 (21-54) days on formula (median, interquartile range)	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
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	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
Healthy infants consuming a standard formula containing corn oil (oral administration)				

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
Ponder et al., 1992	Healthy, full-term infants; n=14; 8 wk	Age: 0 - 3 d 3.24 ± 0.69 kg at baseline 5.15 ± 0.14 kg at end of study	Not specified	Range of intake:101-125 kcal/kg bw/day
De Souza et al., 2017; Leite et al., 2013	Healthy, full-term infants; n=16; 14 d	Age: 108 ± 27 d 3.32 ± 0.33 1 kg birthweight Assume 6.0 kg at end of study (median weight at 3 mo per IOM, 2005)	Not specified	Mean intake: 580 kcal, which corresponds to 95 kcal/kg bw/day assuming median wt at 3 mo
Hayes et al., 1992	Healthy, full-term infants; 0 d n=15; 4 mo	Age: birth 3.51 ± 0.7 at baseline 6.12 ± 0.67 kg at end of study	Not specified	Mean intake: 535 kcal, which corresponds to 111 kcal/kg bw/day assuming midpoint of baseline and end of study weights

Questions #11&12 (Toxicology): (We combine our response to questions 11 and 12 below).

- ***FDA Questions #11&12****:*

  #11 *In the section titled "Clinical Studies of Infants Consuming Corn Oil" beginning on page 29 of the notice, you described the findings of published studies that examined the effects of corn oil-based infant formula in infants, and exposure to complementary food products containing corn oil. However, a safety assessment that employs these findings was not performed. A comparison between the level of exposure to corn oil (or its constituents) in infants from consumption of the proposed exempt infant formula and the exposure to corn oil (or its constituents) in infants found at effect levels in the described published studies is needed to evaluate the safety of the proposed infant formula exposure. Please discuss this safety evaluation as part of your safety narrative.*

  #12 *In the section titled "Phytosterols in the Infant Diet" beginning on page 33 of the notice, you described the findings of published studies and other sources that examined the effects of exposure to phytosterols in food. However, a safety assessment that employs these findings was not performed.*

  A comparison between the level of exposure to phytosterols in infants from consumption of the proposed exempt infant formula and the exposure to phytosterols found at effect levels in the described published studies or sources is needed to evaluate the safety of the proposed infant formula exposure. Please discuss this safety evaluation as part of your safety narrative.

Response to Questions 11&12: As requested by the agency, we now calculate comparisons between the level of exposure to corn oil (or its constituents) in infants from consumption of the proposed exempt infant formula and the exposure to corn oil (or its constituents) in infants found at effect levels in the described published studies to evaluate the safety of the proposed infant formula exposure. For each clinical study referenced in the safety narrative with a quantified amount of corn oil in the formula, the estimated intake of corn oi by infants is calculated below. Based on this estimated intake, the amount of phytosterol provided by the formula is also calculated assuming a concentration of mean phytosterol in corn oil based on analytical data (777 mg per 100 g oil). We present these calculations to compare the specific exposures to corn oil in these studies with the proposed exposure to corn oil (and its constituent, phytosterol) from the intended use in calorically dense formula. In GRN 900 we note that published studies in which corn oil is a component of the fat blend (up to 50%) provide evidence on the suitability of corn oil as a component of the fat blend in infant formula.

As presented on page 22 of the GRAS notification, the estimated intake of corn oil for its intended use is 0.2 g/ kg bw/day at the mean assuming energy intake of 120 kcal/kg bw/day. As detailed above in Question 7, the pseudo-90th percentile intake of 144 kcal/kg bw/day may be more representative of anticipated "high" consumption of the calorically dense formula. Based on these estimates of mean and pseudo-90th percentile formula intake, exposure to corn oil (assuming a maximum of 50% of energy from fat in the formula, and 3% of fat as corn oil),

the mean and pseudo-90th percentile exposure to corn oil are calculated to be 0.20 and 0.24 g/kg bw/day, respectively.

The estimated intake of corn oil from clinical trials among healthy infants that provided the concentration of corn oil in formula or complementary foods is summarized in the Table 4 below. The estimated intake of corn oil by healthy infants consuming corn oil as a component of the fat blend in infant formula ranges from 2.0 to 3.4 g/kg bw/day. In trials that provided corn oil in complementary foods, the estimated corn oil intake ranged from 0.5 to 0.9 g/kg bw/day. The estimated intake of corn oil for its intended use is lower than levels consumed in other clinical trials among healthy infants.

The estimated intake phytosterols from corn oil for its intended use is 1.6 mg/kg bw/day and the mean and 1.9 mg/kg bw/day at the pseudo-90th percentile. The estimated intake of phytosterols from corn oil in clinical trials among infants and children that provided corn oil in formula or complementary foods is summarized in the Table 4 below. The estimated intake of phytosterols from infant formula ranges from 15.5 to 58.8 mg/kg bw/day. In trials that provided corn oil in complementary foods, the estimated corn oil intake ranged from 6.0 to 211 mg/kg bw/day. The estimated intake of phytosterols from corn oil for its intended use is lower than levels consumed in other clinical trials among healthy infants and the JECFA ADI of 40 mg/kg bw/day.

Table 5. Estimated Corn Oil and Phytosterol Intake in Clinical Trials among Healthy Infants

Study	Study Population; Age at Baseline	Corn Oil/Phytosterol Exposure; Intake Duration	Estimated Corn Oil Intake (g/kg bw/day)	Estimated Phytosterol Intake (mg/kg bw/day)	Assumptions*
Exposures from Infant Formula					
Ponder et al., 1992	14 Healthy, full-term infants; 0 - 3 d	infant formula containing 1.8 g corn oil/100 mL; 8 wk	2.75 - 3.4	21.4 - 26.4	Energy density: 67 kcal/100 mL. 3.65 g fat per 100 mL, 50% fat from corn oil Energy Intake: 101 - 125 kcal/day Body Weight: 5.15 kg Phytosterols: 777 mg/100 g corn oil (average of analytical data)
De Souza et al., 2017; Leite et al., 2013	16 Healthy, full-term infants; 108 ± 27 d	infant formula containing 1.4 g corn oil/100 mL; 14 d	2.0	15.5	Energy density: 67 kcal/100 mL Energy intake: 95 kcal/kg (IOM) Body Weight: 6.0 kg (IOM) Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Hayes et al., 1992	15 Healthy, full-term infants; 0 d	infant formula containing 3.1 g corn oil per 100 kcal and 35% kcal from fat, 4 mo	3.4	26.7	Energy as fat: 79.5% fat as corn oil (3.1 g out of of 3.9 g per 100 kcal) Energy Intake: 535 kcal/day Body Weight: 4.8 kg [average of initial (3.509 kg) and final BW (6.123 kg)] Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Mellies et al., 1976	53 Healthy infants or infants with familial hypercholesterolemia; 2 mo	24 oz infant formula containing 26.8 g vegetable oil and 300 mg phytosterols; cross-sectional	-	58.8	Energy Intake: 482 kcal/day Body Weight: 5.1 kg [average of male/female birth - 2 mo (CDC)]
Mellies et al., 1976	53 Healthy infants or infants with familial hypercholesterolemia; 8.5 mo	32 oz infant formula containing 39.0 g vegetable oil and 400 mg phytosterols; cross-sectional	-	48.5	Energy Intake: 1,065 kcal/day Body Weight: 8.25 kg [average of male/female 6 - 8 mo (CDC)]
Exposures from Complementary Foods					
Schwartz et al., 2009	53 Healthy, full-term infants; 4 mo	complementary food containing 3.4 g corn oil; 6 mo	0.5	3.8	Body Weight: 7 kg Phytosterols: 777 mg/100 g corn oil (average of analytical data)
Libuda et al., 2016	72 Healthy, full-term infants; 4 - 6 mo	complementary food containing 2.66 or 3.08 g corn oil; 4 - 6 mo	0.8 or 0.9	6.0-6.9	Food intake: 190 or 220 g Body Weight: 3.46 kg Phytosterols: 777 mg/100 g corn oil (average of analytical

					data)
Tammi et al., 2001	40 Healthy children; 13 mo	low saturated fat & cholesterol diet + vegetable oil or margarine containing 132 mg phytosterols; 1 mo	-	13.1	Body Weight: 10.1 kg
Garoufi et al., 2014	64 Children, 30 with hypercholesterolemia and 34 healthy; 9 mo (range 4.5 - 16)	complementary food containing 2 g phytosterols; 6-12 mo	-	211	Body Weight: 9.5 kg [average of male/female 9-11 mo (CDC)]

% of fat blend from corn oil not reported in Goalwin and Pomeranze, 1962; Uauy et al., 1990; Uauy et al., 1994; Hoffman et al., 1999; Schouten, 2013.

*Values as reported in manuscript or based on assumed values.

Question #13 (Toxicology):

- ***FDA Question #13****: In your amendment from May 1, 2020, which 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)." 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 corn oil ingredient in a calorically-dense formula (i.e., expected to provide more fat per feeding) considering the gastrointestinal abnormalities often found in infants with CF (e.g., Wouthuyzen-Bakker et al., 2011).*

Response to Question 13: 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). 1/ For infants with CF who demonstrate weight loss or inadequate weight gain, calorie-dense feedings are recommended. 2/

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 – 67 kcal/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 when to the current practice.

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 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 calorically density of feedings is recommended. In cases where a calorie-dense feeding is recommended, the fat load of feeding

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1/ 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.

2/ *See id*.

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

Question #14 (Final Formatting):

- ***FDA Question #14****: Please state your conclusion that your intended use of corn oil is GRAS based on the totality of data and information provided in your GRAS notice.*

Response to Question 14: In conclusion, the intended use of corn oil is GRAS based on the totality of data and information provided in the GRAS notice.

Question #15:

- ***FDA Question #15****: The numbering of the tables in the GRAS notice is inaccurate. For example, on page 4 of the notice in the "List of Tables," eleven tables and their titles are listed. However, thirteen tables are presented in the text of the notice. Beginning with Table 9, the table listing is inaccurate, as are some of the references to specific tables in the text of the notice. Please clarify the table listings and provide statements correcting the table references. A revised copy of the affected pages is not necessary.*

Response to Question 15: We apologize for the discrepancy and confusion. Copied below is the correct table reference.

Page	Correction
19	The reference to Table 9 on this page should instead reference Table 11 (which appears on page 20).
20	The table title should be Table 11. Formula Intake in Studies of Term Infants Consuming a Calorically Dense Infant Formula
22	The two references to Table 10 on this page should instead reference Table 12 (which appears on page 22).
22	The table title should be Table 12. Estimated Daily Intake of Corn Oil and Phytosterols from the Maximum Proposed Use of Corn Oil
25	The three references to Table 11 on this page should instead reference Table 13 (which appears on page 26).
26	The table title should be Table 13. Fat and Fatty Acid Requirements in Infant Formula for Term Infants
39	The reference to Table 10 on this page should instead reference Table 12 (which appears on page 22).

* * *

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

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[redacted]

20-05-2020

To whom it may concern

Statement regarding Corn oil [redacted] (Material: 6280)

We hereby confirm that all processing aids and materials which are in contact with this product at [redacted] are food grade and our suppliers adhere to the relevant European legislation. This is supplied [redacted] for infant nutrition use and thus Corn oil (material 6280) complies to [redacted] statement concerning contaminants for oils and fats for infant nutrition.

[redacted] has been assessed and determined to comply with the requirements of FOOD SAFETY SYSTEM CERTIFICATION 22000, please see latest sign certificate for more information.

[redacted]

[redacted]

[redacted]

05-06-2020

To whom it may concern

Statement regarding Corn oil [redacted] (Material: 6280)

With reference to above-mentioned product, Benzopyrenes (BaP) and polycyclic aromatic hydrocarbons (PAHs) comply with the maximum limit permitted for vegetable oils for food and infant formula according to EU legislation EC 1881/2006.

Benzopyrenes (BaP) are polycyclic aromatic hydrocarbons (PAHs), a group of chemical compounds that are formed by the incomplete combustion of organic matter. If present in incoming raw materials, they will be reduced / removed during the bleaching step of the refining process. These compounds are not intentionally introduced or formed during the manufacturing process of corn oil.

Benzopyrenes (BaP) are polycyclic aromatic hydrocarbons (PAHs) are measured as part of [redacted]'s contaminants monitoring programme for oils and fats for infant nutrition, with maximum limits of 1.0µg/kg and 2.0µg/kg respectively.

[redacted].

[redacted]

[redacted]

19-05-2020

To whom it may concern

Statement regarding 3-MCPD in Corn oil [redacted]

For several years, [redacted] has a monitoring program in place specifically for 3-MCPD of our raw materials and end products. The 3-MCPD analysis is performed by a certified external laboratory.

The 3-MCPD guarantee for Corn oil is given in the table below:

Product	Product number	Sum free 3-MCPD, 3-MCPDester, det. as free 3-MCPD (ppm)
Corn oil	6280	Max 0.25

The *AOCS Cd 29b-13 GC/MS* an accredited method suitable for the analysis of vegetable fats and oils and has a limit of quantification (LOQ) of 0.1mg/kg. Commitments made by [redacted] on specific vegetable oil blends are subject to the limitations of the current validated analytical method capabilities. [redacted] continues with optimization to have 3-MCPD levels as low as possible.

[redacted]

[redacted]

[redacted]

Sterol composition of Corn oil (628000)			
Batch no:	2017017	2023678	2028874
Lot no:	2192057	2201158	2209780
Lot date:	2018-12-14	2018-01-03	2018-01-18
Total Sterols	800 mg/100g	750 mg/100g	780 mg/100g
Campesterol	20.6 %	20.3 %	20.4 %
Campestanol	0.9 %	0.7 %	0.9 %
Stigmasterol	6.7 %	7.3 %	6.9 %
Sitostanol	2.6 %	2.1 %	2.4 %
Beta-sitosterol	62.5 %	64.4 %	64.0 %
Delta5-avenasterol	2.0 %	2.8 %	2.7 %
Delta7-stigmasterol	0.3 %	0.1 %	0.2 %
Delta7-avenasterol	1.5 %	1.2 %	1.2 %
Cholesterol	0.2%	0.2%	0.2%
Brassiciasterol	0.7%	0.2%	0.3%

03-06-2020

[redacted]

[redacted]

From:	Tao, Xin
To:	Morissette, Rachel
Cc:	Steinborn, Steven B.
Subject:	RE: additional clarifications requested for GRN 000900
Date:	Tuesday, August 4, 2020 4:08:53 PM
Attachments:	image001.png Response to FDA's Additional Questions for GRN 000900.pdf

Dear Rachel,

Attached, please find our response to the agency's additional questions for GRN 900. Please feel free to reach out if you have any further questions.

Best regards,
Steve and Xin

Xin Tao
Senior Associate

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Please consider the environment before printing this e-mail.

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Thursday, July 30, 2020 9:40 AM
To: Steinborn, Steven B.; Tao, Xin
Subject: RE: additional clarifications requested for GRN 000900

Thanks, Steve!

Best,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
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FDA U.S. FOOD & DRUG ADMINISTRATION

From: Steinborn, Steven B. <steven.steinborn@hoganlovells.com>
Sent: Thursday, July 30, 2020 9:36 AM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>; Tao, Xin <xin.tao@hoganlovells.com>
Subject: RE: additional clarifications requested for GRN 000900

Good morning. Thank you for your careful review and bringing these questions to our attention. Allow us to review, and consult with our client. We will do our best to ensure all of the referenced information is accurate and complete.

Steve

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Thursday, July 30, 2020 9:30 AM
To: Steinborn, Steven B.; Tao, Xin
Subject: additional clarifications requested for GRN 000900

Dear Steve and Xin,

We completed our review of the amendments that you sent and noted several inconsistencies that we request clarification on below.

1. The specified limits summarized below are inconsistent within the main text of GRN 000900 and within Appendices B and C. Please indicate which limits are correct and provide corrected tables and/or a clarification statement as appropriate.

Component	Values in *original text of GRN 900* (Table #, page #))	Values in *original text of GRN 900* (Table #, page #)	*Appendices to GRN 900* (Analytical certificate, table #, page #)
	Table 5, p. 15 of 47	**Table 6, p. 15 of 47**	**Appendix B, 2018 certificates (pp. 2-5 of 9), Table B-1 p. 6 of 9**
C16:0 (%)	9-13	8-13	9-13
C18:0 (%)	1-3	1-4	1-3
C18:2 (%)	49-62.0	52-62	49-62.0
C18:3 (%)	≤2.0%	≤2.2%	≤2.0%
Peroxide value (mEq/kg)	NMT 0.5	NMT 1	NMT 0.5
	Table 5, p. 15 of 47	**Table 7, p. 16 of 47**	**Appendix C, 2018 statement (p. 5 of 10), "Metals" table**
Arsenic (mg/kg)	NMT 0.5	NMT 0.1	NMT 0.1

Lead (mg/kg)	NMT 0.1	NMT 0.01	NMT 0.01

2. In Table 10 (p. 17 of original GRN 000900 text): Please confirm that the **Sum of 6 PCBs** includes values for PCB180 and not "PCB18" as stated.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Regulatory Review Scientist

Division of Food Ingredients
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Via Electronic Mail

August 4th, 2020

Rachel Morissette, Ph.D.
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Re: Response to FDA's Additional Questions for GRN 000900

Dear Dr. Morissette,

We hereby submit our responses to FDA's additional questions for GRAS Notice 000900 (GRN 900), which covers the intended use of corn oil as a source of fat 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:

- ***FDA Question #1****: The specified limits summarized below are inconsistent within the main text of GRN 000900 and within Appendices B and C. Please indicate which limits are correct and provide corrected tables and/or a clarification statement as appropriate.*

Component	*Values in original text of GRN 900 (Table #, page #))*	*Values in original text of GRN 900 (Table #, page #)*	*Appendices to GRN 900 (Analytical certificate, table #, page #)*
	Table 5, p. 15 of 47	***Table 6, p. 15 of 47***	***Appendix B, 2018 certificates (pp. 2-5 of 9), Table B-1 p. 6 of 9***

C16:0 (%)	*9-13*	*8-13*	*9-13*
C18:0 (%)	*1-3*	*1-4*	*1-3*
C18:2 (%)	*49-62.0*	*52-62*	*49-62.0*
C18:3 (%)	*≤2.0%*	*≤2.2%*	*≤2.0%*
Peroxide value (mEq/kg)	*NMT 0.5*	*NMT 1*	*NMT 0.5-*
	Table 5, p. 15 of 47	***Table 7, p. 16 of 47***	***Appendix C, 2018 statement (p. 5 of 10), "Metals" table***
Arsenic (mg/kg)	*NMT 0.5*	*NMT 0.1*	*NMT 0.1*
Lead (mg/kg)	*NMT 0.1*	*NMT 0.01*	*NMT 0.01*

Response to Question 1: We apologize for the confusion caused by the inconsistency of the limits provided in the Tables 5, 6, and 7 of the original submission. Other than lead, the correct and current specification values should be those reported in Appendix B and Appendix C of GRN 900. For lead, the correct specification is "NMT 0.015 mg/kg" and the ingredient supplier will adopt a new specification of "NMT 0.01 mg/kg" in Q1 of 2021.

For your easy reference, we have added a new column to the FDA table with these correct values below for clarification. The batch analysis data of the corn oil ingredients submitted in GRN 900 also show all these specifications are being met.

Component	Values in original text of GRN 900 (Table #, page #))	Values in original text of GRN 900 (Table #, page #)	Appendices to GRN 900 (Analytical certificate, table #, page #)	Correct Specification Values
	Table 5, p. 15 of 47	**Table 6, p. 15 of 47**	**Appendix B, 2018 certificates (pp. 2-5 of 9), Table B-1 p. 6 of 9**	
C16:0 (%)	9-13	8-13	9-13	9-13

C18:0 (%)	1-3	1-4	1-3	1-3
C18:2 (%)	49-62.0	52-62	49-62.0	49-62
C18:3 (%)	≤2.0%	≤2.2%	≤2.0%	≤2.0%
Peroxide value (mEq/kg)	NMT 0.5	NMT 1	NMT 0.5	NMT 0.5
	Table 5, p. 15 of 47	**Table 7, p. 16 of 47**	**Appendix C, 2018 statement (p. 5 of 10), "Metals" table**	
Arsenic (mg/kg)	NMT 0.5	NMT 0.1	NMT 0.1	NMT 0.1
Lead (mg/kg)	NMT 0.1	NMT 0.01	NMT 0.01	NMT 0.015

- ***FDA Question #2****: In Table 10 (p. 17 of original GRN 000900 text): Please confirm that the Sum of 6 PCBs includes values for PCB180 and not "PCB18" as stated.*

Response to Question 2: We hereby confirm the Sum of 6 PCB values reported in Table 10 of GRN 900 should include values for "PCB180" and not "PCB18" as originally stated. We apologize for any confusion caused by this typo.

* * *

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

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.