KEMIN® INSPIRED MOLECULAR SOLUTIONS™

Kemin Industries, Inc.
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March 19, 2018

Dr. Paulette Gaynor
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

Dear Dr. Gaynor,

Re: GRAS Notice for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate)

In accordance with 21 CFR §170 Subpart E consisting of §170.203 through 170.285, Kemin Industries, Inc. (d/b/a Kemin Food Technologies) hereby informs the United States Food and Drug Administration of the conclusion that the intended use of Oil-Soluble Green Tea Extract (OS-GTE; Green Tea Catechin Palmitate) as an antioxidant in various food products is Generally Recognized as Safe (GRAS), based on scientific procedures. Information setting forth the basis for this GRAS conclusion are presented in the enclosed notice. The intended use of OS-GTE as an antioxidant in foods is therefore not subject to the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act.

Included in this submission is one paper copy of the GRAS notice, as well as a compact disc (CD) that contains an electronic copy of all enclosed files. The electronic and paper copies of the GRAS notice are identical. The enclosed electronic files were scanned for viruses prior to submission and are certified as being virus-free.

Should you have any questions or concerns regarding this GRAS notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner.

Yours sincerely,

(b) (6)

Sylvia A. Bergman, Ph.D.
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies

GRAS NOTICE FOR OIL-SOLUBLE GREEN TEA EXTRACT (GREEN TEA CATECHIN PALMITATE)

Prepared for:
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 USA

Prepared by:
Kemin Industries, Inc. d/b/a Kemin Food Technologies
2100 Maury Street
Des Moines, IA
50317 USA

March 19, 2018

GRAS Notice for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate)

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GRAS Notice for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate)

Part 1. §170.225 Signed Statements and Certification

In accordance with 21 CFR §170 Subpart E consisting of §170.203 through 170.285, Kemin Industries, Inc. (d/b/a Kemin Food Technologies and referred to hereafter as "Kemin") hereby submits a Generally Recognized as Safe (GRAS) notice to the United States (U.S.) Food and Drug Administration (FDA) for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate). It is Kemin's view that Oil-Soluble Green Tea Extract is not subject to the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act, on the basis of their conclusion that Oil-Soluble Green Tea Extract is GRAS under its intended conditions of use. In addition, as a responsible official of Kemin, I hereby certify that all data and information presented in this notice constitute a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to Kemin and pertinent to the evaluation of the safety and GRAS status of palmitoylated green tea catechins for addition to foods, as described herein.

Signed,

(b) (6)

March 19, 2018

Sylvia A. Bergman, Ph.D. Date
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies

1.1 Name and Address of Notifier

Sylvia A. Bergman, Ph.D.
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies
2100 Maury Street
Des Moines, IA
50317 USA

1.2 Common Name of Notified Substance

Oil-Soluble Green Tea Extract (abbreviated as OS-GTE). OS-GTE is also known by the following synonyms: Lipid-Soluble Green Tea Extract, Green Tea Catechin Palmitate, Oil-Soluble Tea Polyphenol, Palmitic Ester of Green Tea Extract, Green Tea Extract (OS), Green Tea Extract.

1.3 Conditions of Use

Oil-Soluble Green Tea Extract (OS-GTE) has been shown to be efficacious as lipophilic antioxidant in foods, and accordingly it may be used to maintain the stability and shelf-life of fat-containing foods (Patent WO 2013036934 A1 – Cutler *et al*., 2013).

The intended food uses and use levels of OS-GTE as an antioxidant in foods are listed below in Table 1.3-1. OS-GTE is intended for addition to a variety of conventional foods in the U.S. at use levels ranging from 0.05 to 0.28% (500 to 2,800 ppm). Of note, Kemin does not intend to market OS-GTE as an antioxidant in meat and poultry products that are subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA), or to foods that are promoted specifically towards infants and young children. Additionally, some of the foods listed in Table 1.3-1 have a standard of identity within Title 21 of the Code of Federal Regulations (CFR). OS-GTE is not intended for addition to standardized foods, unless it is allowed for by the applicable standard of identity.

Table 1.3-1 Intended Food Uses and Use Levels for OS-GTE in the U.S.

Food Category (21 CFR §170.3 – U.S. FDA, 2017a)	Intended Food Uses[a]	Maximum Intended Use Level of OS-GTE in Foods (%)
Baked Goods and Baking Mixes	Biscuits	0.05
	Cookies	0.05
	Crackers	0.05
	Pizza Crust	0.05
Breakfast Cereals	Instant and Regular Hot Breakfast Cereals	0.10
	Ready-to-Eat Breakfast Cereals	0.20
Cheeses	Processed Cheese	0.10
Confections and Frostings	Frosting, Icings, and Coatings	0.05
Dairy Product Analogs	Coffee Whiteners	0.05
Fats and Oils	Butter	0.28
	Fat-Based Sauces	0.28
	Margarine[b] and Margarine-like Spreads	0.28
	Mayonnaise[b] and Mayonnaise-Type Dressings	0.05
	Oils	0.28
	Salad Dressings[b]	0.10
Grain Products and Pastas	Cereal and Granola Bars	0.15
	Energy Bars, Meal Replacement Bars, and Fortified Bars	0.15
	Noodle Products	0.05
Herbs, Seeds, Spices, Seasonings, Blends, Extracts, and Flavorings	Spices, Seasonings, and Blends	0.28
Nut and Nut Products	Nut Spreads	0.10
	Processed Whole Nuts, Coated Nuts, and Mixtures	0.28
Snack Foods	Snack Foods	0.10
Soft Candy	Chocolate Confectionary	0.05

CFR = Code of Federal Regulations; OS-GTE = Oil-Soluble Green Tea Extract; U.S. FDA = United States Food and Drug Administration; U.S. = United States.

[a] OS-GTE is not intended for use in meat and poultry products that are regulated by the FSIS of the USDA.

[b] These foods have a standard of identity within Title 21 of the CFR. OS-GTE is not intended for addition to standardized foods unless permitted by the regulations.

1.4 Basis for GRAS

Pursuant to § 170.30 (a) and (b) in Title 21 of the CFR (U.S. FDA, 2017a), Kemin's Oil-Soluble Green Tea Extract has been concluded to have GRAS status for use as an antioxidant in specified conventional food products, as described in Part 1.3 of this notice, on the basis of scientific procedures.

1.5 Availability of Information

Kemin agrees to make the data and information that are the basis for the conclusion of the GRAS status for palmitoylated green tea catechins available to the FDA, either during or after the evaluation of the GRAS notice. This data and information will be available for review and copy upon request at the address specified below during business hours:

Kemin Food Technologies
2100 Maury Street
Des Moines, IA
50317 USA

In addition, upon request, Kemin will provide the FDA with a complete copy of the data and information that are the basis for the conclusion of the GRAS status for Oil-Soluble Green Tea Extract, either in an electronic format that is accessible for the FDA's evaluation, or on paper.

1.6 Freedom of Information Act, 5 U.S.C. 552

It is Kemin's view that all data and information presented in Parts 2 through 7 of this notice do not contain any trade secret, commercial, or financial information that are privileged or confidential. Therefore, none of the data and information presented herein are exempt from the Freedom of Information Act, 5 U.S.C. Section 552.

1.7 Food Safety and Inspection Service Statement

Kemin does not intend to market Oil-Soluble Green Tea Extract as an antioxidant in meat and poultry products that are subject to regulation by the FSIS of the USDA.

Part 2. §170.230 Identity, Method of Manufacture, Specifications, and Physical or Technical Effect

2.1 Identity

2.1.1 Common or Usual Name

Common Name: Oil-Soluble Green Tea Extract (abbreviated as OS-GTE)

Examples of Synonyms: Lipid-Soluble Green Tea Extract, Green Tea Catechin Palmitate, Catechin Palmitate Esters, Palmitic Ester of Green Tea Extract, Lipid Soluble Tea Polyphenol, Palmitoylated Green Tea Extract, Palmitoylated *Camilla sinensis* Extract, Palmitoylated Green Tea Extract Catechins, Green tea extract (OS), and Green tea extract.

2.1.2 Trade Name

OS-GTE is blended with suitable carriers to produce the commercially available formulations that may be marketed by Kemin under brand names such as GT-FORT™, Fortium®, EN-FORT™, NaturFORT™, *etc*. These formulations are sold only to other manufacturers for incorporation into finished foods, and not directly to consumers.

2.1.3 Chemical Name

Not applicable.

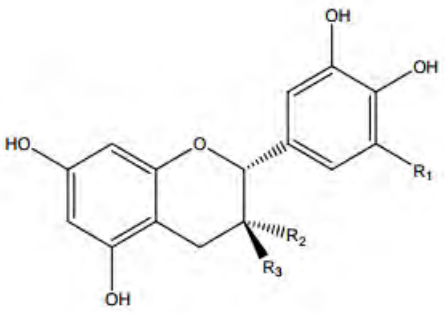
2.1.4 Chemical Abstract Service (CAS) Number

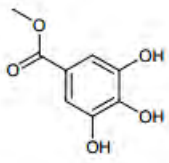
1448315-04-5

2.1.5 Structural Formula

Tea produced from the leaves of the *Camellia sinensis* (L.) Kuntze (*Thea sinensis* L.) plant is a heterogeneous mixture of polyphenols, with the monomeric flavan-3-ols being the predominant form, accounting for approximately 30 to 40% of the leaf dry weight (Balentine *et al.*, 1997; Vuong *et al.*, 2010; Abdel-Rahman *et al.*, 2011; Clifford *et al.*, 2013). The primary flavan-3-ols present in green tea are often broadly referred to as "green tea catechins". Flavan-3-ols have 2 chiral centers (*i.e.*, at C2 and C3) and therefore can exist as 4 different diastereoisomers (Tsao, 2010). The isomeric forms that are in the *cis* configuration are denoted with an "epi" prefix in their nomenclature (*e.g.*, epicatechin), while those in the *trans* configuration do not contain this prefix (*e.g.*, catechin) (Tsao, 2010). The predominant flavan-3-ols that are present in green tea leaves and their aqueous infusions include (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epigallocatechin gallate (EGCG) (Seto *et al.*, 1997; Feng, 2006; Clifford *et al.*, 2013; Blumberg *et al.*, 2015). Smaller amounts of other flavan-3-ols such as (+)-catechin, (+)-catechin gallate (CG), (+)-gallocatechin (GC) and (+)-gallocatechin gallate (GCG) may also be present (Feng, 2006; Clifford *et al.*, 2013; Blumberg *et al.*, 2015). The chemical structures of these flavan-3-ols are presented in Figure 2.1.5-1.

Figure 2.1.5-1 Chemical Structures of the Predominant Flavan-3-ols in Green Tea (Taken from Bhagwat *et al.*, 2014)



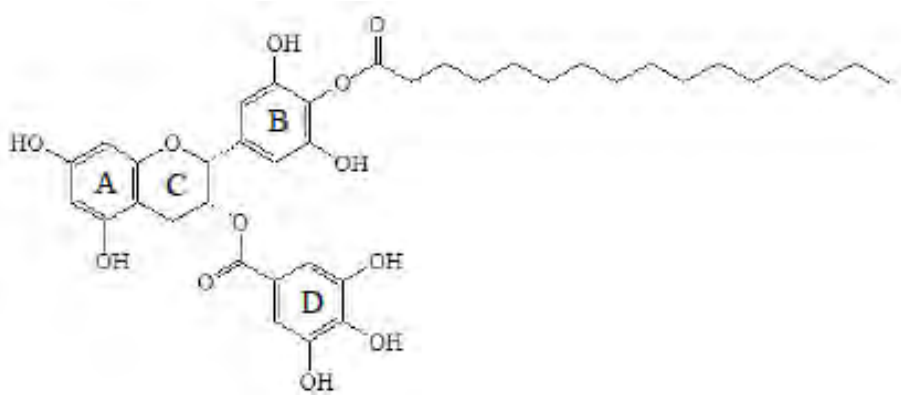


Gallate

Flavan-3-ol	R_1	R_2	R_3
(+)-Catechin (C)	H	H	OH
(+)-Catechin-3-gallate (CG)	H	H	Gallate
(-)-Epicatechin (EC)	H	OH	H
(-)-Epicatechin-3-gallate (ECG)	H	Gallate	H
(-)-Epigallocatechin (EGC)	OH	OH	H
(-)-Epigallocatechin-3-gallate (EGCG)	OH	Gallate	H
(+)-Gallocatechin (GC)	OH	H	OH
(+)-Gallocatechin-3-gallate (GCG)	OH	H	Gallate

Oil-Soluble Green Tea Extract is manufactured by reacting green tea catechins with a source of palmitic acid in the presence of a catalyst (see Part 2.2). The green tea catechins can be acylated at any one of its hydroxyl groups. Although the main green tea catechins contain between 5 to 8 hydroxyl groups, all of which can be theoretically palmitoylated, only mono-, di- and tri-palmitoyl catechins have been detected in Kemin's OS-GTE. Palmitoylated catechins containing 4 or more palmitates have not been identified; this is likely due to factors related to chemical reactivity and steric restriction. The structure of one palmitoylated form of green tea catechins (*i.e.*, EGCG monopalmitate) is presented in Figure 2.1.5-2 below as a representative example.

Figure 2.1.5-2 Chemical Structure of One Possible Form of EGCG Monopalmitate



2.1.6 Compositional Analysis

Kemin has conducted extensive analyses to characterize the composition of their OS-GTE material. As shown in Table 2.1.6-1, OS-GTE is largely composed of palmitoylated catechins (66 to 82%, expressed as EGCG monopalmitate equivalents). Given the complex nature of the material (*i.e.*, mixture of isomers with closely related structures), the quantification of each individual palmitoylated catechins in Kemin's material is not feasible by current chromatography methods. To overcome this analytical shortcoming, Kemin has developed a colorimetric assay to approximate the content of palmitoylated catechins present. This assay is a spectrophotometric method involving ferrous tartrate, which forms a colored complex with polyphenols (Wang *et al.*, 1997). The optical absorbance of the iron (II)-polyphenol complex at 520 nm is measured and quantified against an ethyl gallate standard, which is then converted to an EGCG monopalmitate basis using the ratio of their molar masses. EGCG monopalmitate was selected for this derivation as it is the most representative species in the OS-GTE mixture (see Table 2.1.6-2). As such, the concentration determined by this method is not an exact quantification of the total palmitoylated catechins present, but rather, it represents the content of palmitoylated catechins expressed as EGCG monopalmitate equivalents.

The remainder of Kemin's material is accounted for by free palmitic acid (approximately 11 to 15% w/w), and small amounts of free catechins, gallic acid, and alkaloids (caffeine, theobromine, and theophylline), which is less than 2% w/w combined. Other residuals (*e.g.*, moisture, ash, and protein) account for 2 to 6% w/w.

Table 2.1.6-1 Composition of Kemin's OS-GTE

Parameters	**Lot Number**		
	20111227	**12072209**	**12082407**
Assay for palmitoylated catechins (% expressed as EGCG monopalmitate equivalents)	**75.17**	**72.39**	**75.09**
Free palmitic acid (% w/w)	**12.22**	**13.74**	**11.08**
Free catechins and gallic acid (% w/w)			
Gallic acid	0.399	0.068	0.075
EGC	Below LOD[a]	Below LOD[a]	Below LOD[a]
EGCG	0.205	0.318	0.260
GCG	0.289	0.304	0.332
ECG	0.069	0.083	0.082
CG	0.141	0.156	0.186
Total free catechins and gallic acid	**1.103**	**0.929**	**0.936**
Alkaloids (% w/w)			
Theobromine	0.142	0.085	0.103
Theophylline	0.009	0.001	0.002
Caffeine	0.157	0.095	0.115
Total alkaloids	**0.307**	**0.181**	**0.219**
Proximate analysis (% w/w)			
Ash	0.50	0.46	0.66
Crude Fiber	<0.2	<0.2	<0.2
Moisture	3.71	2.00	1.80
Proteins	0.78	0.52	0.60
Starches	<0.01	0.20	0.90
Unsaponifiable matter	0.21	0.02	0.02

Table 2.1.6-1 Composition of Kemin's OS-GTE

Parameters	Lot Number		
	20111227	12072209	12082407
Total proximates	**5.59**	**3.60**	**4.47**

CG = catechin gallate; ECG = epicatechin gallate: EGC = epigallocatechin; EGCG = epigallocatechin gallate; GCG = gallocatechin gallate; LOD = limit of detection; OS-GTE = Oil-Soluble Green Tea Extract.
[a] The limit of detection is 0.0042 mg/mL.

Additionally, Kemin has determined the compositional breakdown of OS-GTE according to the degree of palmitoyl substitution for the individual green tea catechins, as summarized in Table 2.1.6-2. The analysis was conducted on the same 3 production lots of OS-GTE that were characterized in Table 2.1.6-1. The data were obtained by ultra-performance liquid chromatography with photodiode array and mass spectroscopy detection (UPLC-PDA/MS). Due to the nature of the analytical technique, wherein it was assumed that all forms of palmitoylated catechins have the same ionization efficiency, the values reported are not exact, but rather, represent a semi-quantitative estimate. As mentioned in Part 2.1.5, the primary flavan-3-ols in green tea are EGCG, ECG, EGC, and EC; accordingly, these are the main palmitoylated catechins present in OS-GTE. The mono-, di-, and tri-palmitates of EGCG accounts for approximately 50% of the palmitoylated catechins, with EGCG monopalmitate being the predominant species present (Table 2.1.6-2). The majority of the palmitoylated catechins are in the monopalmitate form (approximately 65 to 68%), with lesser amount of dipalmitates (approximately 29 to 33%) and tripalmitates (approximately 3%) present. Based on the molar masses of the different mono-, di-, and tri-palmitates of the individual green tea catechins and the molar masses of the unesterified catechin forms, it is estimated that approximately 57% w/w of the total palmitoylated catechins in OS-GTE is accounted for by its green tea catechins component[1], while the remainder represents palmitic acid. It is also estimated that approximately 30% w/w of the total palmitoylated catechins content is EGCG[2].

Furthermore, Kemin has demonstrated that there is minimal variability in the high-performance liquid chromatography (HPLC) fingerprint profile of 10 different lots of OS-GTE, suggesting the manufacturing process consistently produces a material with similar proportions of catechin mono-, di-, and tri-palmitates. Kemin also notes that the content of palmitoylated catechins was generally consistent across 17 non-consecutive batches of OS-GTE produced between 2010 to 2017, with the reported values remaining within the specified range of 66 to 82% (expressed as EGCG monopalmitate equivalents).

[1] Calculated as follows: (Content of an individual palmitoylated catechin form as a proportion of total palmitoylated catechins) x (1/molar mass of the individual palmitoylated catechin form) x (molar mass of the unesterified catechin form).
[2] Based on the molar masses of the mono-, di-, and tri-palmitates of EGCG (ranging 696.77 to 1,173.57 g/mol) and its unesterified form (458.372 g/mol), the amount of EGCG contributed by its mono-, di-, and tri-palmitates represents approximately 19%, 10%, and 0.5%, respectively, of the total palmitoylated catechin content on a weight-by-weight basis. Accordingly, the sum of the EGCG contributed by its mono-, di-, and tri-palmitate forms is approximately 30% w/w of the total palmitoylated catechin content.

Table 2.1.6-2 Compositional Breakdown by Degree of Palmitoyl Substitution

Catechin Species	Content as a Proportion of Total Palmitoylated Catechins (% w/w)[a]			
	Monopalmitate	Dipalmitate	Tripalmitate	Total
Lot #20111227				
EGCG	28.6%	20.9%	1.2%	**50.6%**
ECG	17.3%	6.4%	0.5%	**24.2%**
EGC	6.6%	3.1%	0.4%	**10.1%**
EC	12.0%	2.6%	0.5%	**15.1%**
Total	**64.5%**	**33.0%**	**2.5%**	**100.0%**
Lot #12072209				
EGCG	28.1%	16.7%	1.4%	**46.1%**
ECG	19.2%	5.2%	0.6%	**25.0%**
EGC	7.8%	3.6%	0.6%	**12.1%**
EC	13.3%	3.1%	0.4%	**16.8%**
Total	**68.4%**	**28.6%**	**3.0%**	**100.0%**
Lot #12082407				
EGCG	25.8%	19.5%	1.5%	**46.8%**
ECG	20.6%	6.0%	0.4%	**27.1%**
EGC	5.9%	3.5%	0.7%	**10.1%**
EC	12.4%	3.4%	0.4%	**16.1%**
Total	**64.7%**	**32.4%**	**2.9%**	**100.0%**

EC = epicatechin; ECG = epicatechin gallate; EGC = epigallocatechin; EGCG = epigallocatechin gallate.

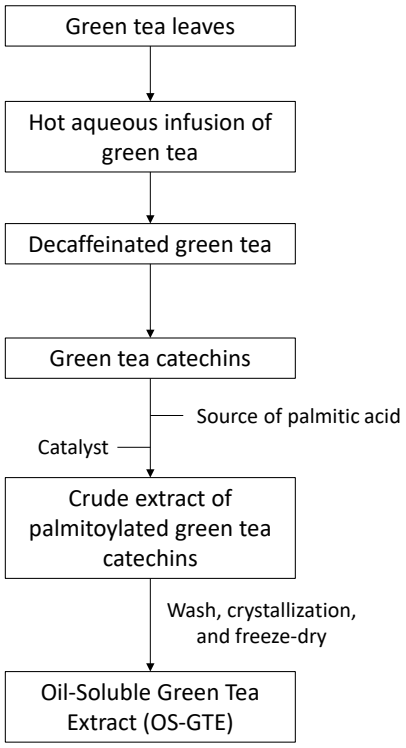
[a] The values presented here were derived using ultra-performance liquid chromatography with photodiode array and mass spectroscopy detection (UPLC-PDA/MS). The analytical method does not differentiate between the *cis*- and *trans*- isomers of each catechin. As such, the values presented in this table includes both forms (*i.e.*, "EGCG" represents both epigallocatechin gallate and gallocatechin gallate; "ECG" represents both epicatechin gallate and catechin gallate, "EGC" represents both epigallocatechin and gallocatechin, and "EC" represents both epicatechin and catechin).

2.2 Method of Manufacture

The manufacturing process for OS-GTE is conducted consistent with current Good Manufacturing Practice (cGMP), and a Hazard Analysis and Critical Control Points (HACCP) system is in place. A schematic overview of the manufacturing process for Kemin's OS-GTE is presented in Figure 2.2-1. In brief, OS-GTE is obtained from a decaffeinated hot aqueous infusion of green tea leaves (*Camellia sinensis* L.*, Thea sinensis* L.). A concentrated extract of green tea catechins is obtained by solvent extraction. The concentrated extract is then reacted with a source of palmitic acid in the presence of a catalyst, followed by a series of washing and purification steps. The extract is concentrated by evaporation, then crystallized and freeze-dried. The resulting OS-GTE material is blended with suitable carriers to produce the commercially marketed formulations.

To produce OS-GTE, Kemin uses green tea leaves that meet acceptable food-grade specification limits established for heavy metals, microbials, and other potential contaminants (*e.g.*, pesticides, dioxins, and mycotoxins). Moreover, all processing aids used in the manufacture of OS-GTE meet appropriate food-grade specifications. OS-GTE does not contain any levels of residual solvents that are of concern.

Figure 2.2-1 Flowchart of the Manufacturing Process for OS-GTE



2.3 Product Specifications and Batch Analyses

2.3.1 Product Specifications

The product specifications that have been established for OS-GTE are presented in Table 2.3.1-1. The specifications include parameters related to the identity and composition of OS-GTE, as well as maximum limits for the levels of heavy metals and microbial contaminants. OS-GTE is specified to contain 66 to 82% palmitoylated catechins, expressed as EGCG monopalmitate equivalents. The material is also specified to contain ≤5% moisture content, and ≤1% of residual ash.

Table 2.3.1-1 Product Specifications for OS-GTE

Parameter	Specification Limit	Method of Analysis
Characteristic Properties		
Assay for palmitoylated catechins (%)[a]	66 to 82	Internal (spectrophotometric method)
Moisture (%)	Max. 5	GB/T 5009.3
Ash (%)	Max. 1	GB/T 5009.4
Antioxidant capacity (as Trolox equivalent)	Min. 160	Internal (CUPRAC assay)
Heavy Metals		
Arsenic (ppm)	Max. 2	GB/T 5009.11
Cadmium (ppm)	Max. 1	GB/T 5009.15
Mercury (ppm)	Max. 0.1	GB/T 5009.17
Lead (ppm)	Max. 1	GB/T 5009.12

Table 2.3.1-1 Product Specifications for OS-GTE

Parameter	Specification Limit	Method of Analysis
Microbiological Contaminants		
Total plate count (CFU/g)	Max. 1,000	GB 4789.2
Yeast and mold (CFU/g)	Max. 100	GB 4789.15
Coliforms (MPN/g)	Max. 3	GB 4789.3
Escherichia coli (MPN/g)	Max. 0.3	GB 4789.38
Salmonella (/25 g)	Not detected	GB 4789.4

CFU = colony forming units; CUPRAC = cupric reducing antioxidant capacity; max. = maximum; min. = minimum; OS-GTE = Oil-Soluble Green Tea Extract; MPN = most probable number; ppm = parts per million.
[a] Expressed as EGCG monopalmitate equivalents.

2.3.2 Batch Analysis

The results of analysis conducted on 3 non-consecutive batches of OS-GTE are summarized in Table 2.3.2-1. The results indicate that the manufacturing process for Kemin's OS-GTE produces a consistent product that conforms to the specifications defined above in Table 2.3.1-1.

Table 2.3.2-1 Analytical Data from 3 Non-Consecutive Batches of OS-GTE

Parameter	Specification Limit	Batch No.		
		2017010401	**1312110858**	**1401101345**
Characteristic Properties				
Assay (%)[a]	66 to 82	75.17	77.89	77.54
Moisture (%)	Max. 5	1.18	1.82	2.00
Ash (%)	Max. 1	0.04	0.048	0.036
Antioxidant capacity (as Trolox equivalent)	Min. 160	182.31	218.88	193.59
Heavy Metals				
Arsenic (ppm)	Max. 2	<0.01	<0.01	0.013
Cadmium (ppm)	Max. 1	<0.005	<0.005	<0.005
Mercury (ppm)	Max. 0.1	<0.01	<0.001	0.002
Lead (ppm)	Max. 1	<0.005	0.024	0.031
Microbiological Contaminants				
Total plate count (CFU/g)	Max. 1,000	<10	<10	<10
Yeast and mold (CFU/g)	Max. 100	<10	<10	<10
Coliforms (MPN/g)	Max. 3	<3	<3	<3
Escherichia coli (MPN/g)	Max. 0.3	Not detected	<0.3	<0.3
Salmonella (/25 g)	Not detected	Not detected	Not detected	Not detected

CFU = colony forming units; OS-GTE = Oil-Soluble Green Tea Extract; max. = maximum; min. = minimum; MPN = most probable number; ppm = parts per million.
[a] Expressed as EGCG monopalmitate equivalents.

2.3.3 Other Contaminants

Kemin routinely conducts analysis on batches of the OS-GTE to ensure that the levels of residual solvents, residual catalyst, dioxins, polychlorinated biphenyls (PCBs), and pesticides remain within acceptable limits.

The results of analysis conducted on 3 batches of the OS-GTE are presented in Table 2.3.3-1. The levels of pesticides in OS-GTE are below the limits of detection. With regards to other contaminants, their residual levels remaining in OS-GTE are either below the limits of detection or do not pose any safety concerns. For instance, assuming that OS-GTE will be added to foods at maximum levels of 0.28%, the maximum amount of carry-over of non-dioxin like PCBs into foods containing OS-GTE is estimated[3] at 0.028 µg/kg. These levels are magnitudes less than the temporary tolerances for PCB residues[4] in foods established in 21 CFR §109.30 (U.S. FDA, 2017a), which range from 0.2 ppm (200 µg/kg) in infant foods and junior foods, to up to 3 ppm (3,000 µg/kg) in poultry on a fat basis.

Table 2.3.3-1 Analytical Data for Other Relevant Contaminants in OS-GTE

Parameter	Acceptable Limit	Method of Analysis	Batch No.		
			2017010401	1312110858	1401101345
Dioxins, PCBs, Pesticides					
Sum of dioxins (2005 WHO-PCDD/F TEQ) (pg/g)[c]	Max. 0.75	EPA 1668 (HRGC/HRMS) and EPA 1613 (HRGC/HRMS)	0.376	0.35	0.59
Sum of dioxins/dioxin-like PCBs (2005 WHO-PCDD/F+PCB TEQ) (pg/g)[c]	Max. 1.25		0.583	0.36	0.61
Non-dioxin PCBs (2005 WHO TEQ; ICES-6) (µg/kg)[c]	Max. 10	Commission Regulation (EU) No 252/2012 in food; Commission Regulation (EU) No 278/2012 in feed	2.00	0.84	2.00
Pesticides	Not detected	LC-MS/MS	Not detected	Not detected	Not detected

EPA = Environmental Protection Agency; EU = European Union; HRGC/HRMS = high resolution gas chromatography/high resolution mass spectrometry; LC-MS/MS = liquid chromatography-tandem mass spectrometry; OS-GTE = Oil-Soluble Green Tea Extract; max. = maximum; PCBs = polychlorinated biphenyls; TEQ = toxic equivalency factor; WHO = World Health Organization.
[a] Limit of detection is 10 ppm.
[b] Limit of detection is 5 ppm.
[c] The values in this table represent the upper-bound TEQ.

2.4 Stability

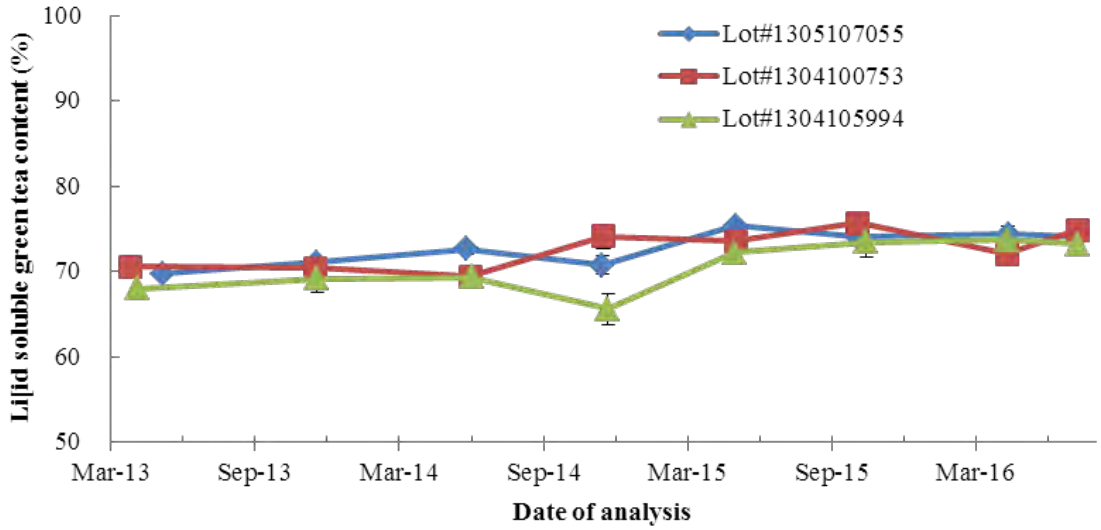
Kemin has investigated the stability of OS-GTE, when it is stored in the dark under ambient conditions (*i.e.*, room temperature) for up to 3 years. As demonstrated in Figure 2.4-1, the content of palmitoylated catechins (expressed as EGCG monopalmitate equivalent), moisture content, and antioxidant capacity remained stable over time. Therefore, OS-GTE is expected to be stable, when it is kept in bulk storage for at least 3 years under ambient conditions in its original packaging.

Additionally, Kemin has preliminary data to support that antioxidant capacity, as measured by the cupric reducing antioxidant capacity (CUPRAC) assay, was not affected when 3 different lots of OS-GTE were kept in an oil matrix at ambient temperatures (22 to 24°C) for durations ranging from 13 to 24 months of storage (data not shown).

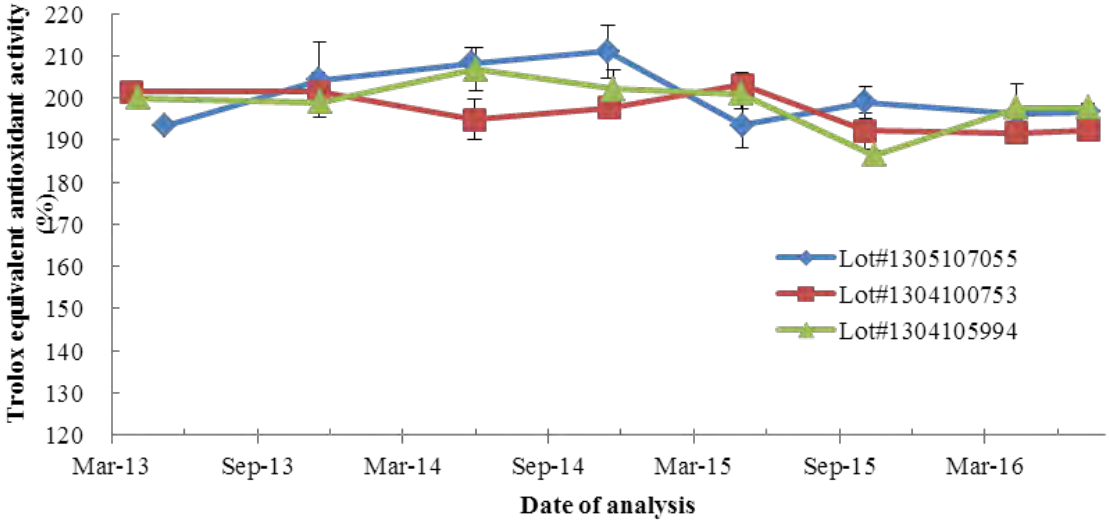
[3] Calculated as the maximum acceptable limit for non-dioxin-like PCBs in OS-GTE (10 µg/kg), multiplied by 0.28%. While residual amounts of dioxin-like PCBs may be present, the maximum acceptable limit for the sum of dioxins/dioxin-like PCBs is set at 1.25 pg/g (0.00125 µg/kg), which is much less than the amount of non-dioxin-like PCBs present.
[4] In 21 CFR §109.30 (U.S. FDA, 2017a), the term "polychlorinated biphenyls (PCB's)" is applicable to mixtures of chlorinated biphenyl compounds, irrespective of which mixture of PCBs is present as the residue.

Figure 2.4-1 Stability of OS-GTE when Kept at Bulk Storage Under Ambient Conditions for 3 Years

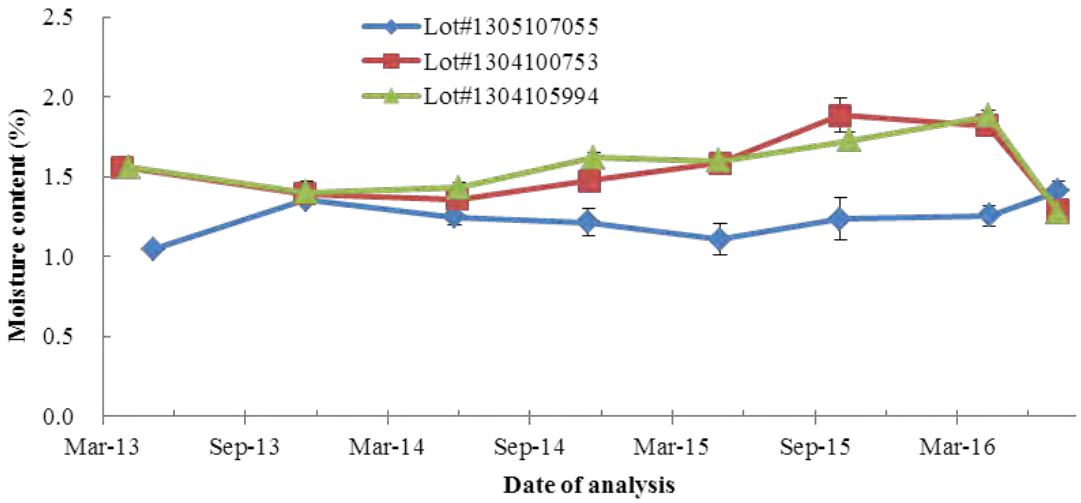
A) Content of Palmitoylated Catechins (EGCG Monopalmitate Equivalents)



B) Antioxidant Activity



C) Moisture Content



Part 3. §170.235 Dietary Exposure

3.1 Existing Dietary Intake

3.1.1 Naturally Occurring Palmitoylated Green Tea Catechins

In addition to the native water-soluble forms of catechins that are extracted from traditional preparations of green tea leaves (*i.e.*, hot aqueous infusions), naturally occurring lipid-conjugated catechins, including palmitoylated catechins, have been detected in dried green tea leaves (Myers *et al.*, 2013). However, the levels of palmitoylated catechins in multiple green tea cultivars were reported to range from 0.02 to 0.09 mg/kg dry weight of green tea leaf, which corresponds to only <0.1% of the total catechins present (Myers *et al.*, 2013). As such, the dietary intake of palmitoylated catechins from their natural occurrence in green tea products is minimal when compared to the intake of their free, unconjugated counterparts.

3.1.2 Current Uses of OS-GTE

Uses of OS-GTE as a Flavor Modifier in the U.S.

The Flavor Extract Manufacturers Association (FEMA) Expert Panel has concluded the intended uses of OS-GTE (FEMA No. 4812) as a flavor modifier in foods to be GRAS (Cohen *et al.*, 2015a,b; Cohen *et al.*, 2017). OS-GTE may be used to modify the overall flavor and/or taste profile in creamy, buttery, and sweet foods (*i.e.*, to reduce excessive sweetness or buttery tastes in foods) (FEMA, 2016). The FEMA Expert Panel first evaluated the intended use of OS-GTE as a flavor modifier in 2015, wherein the average usual use levels were reported to range from 50 to 250 ppm, and the average maximum use levels range from 75 to 500 ppm (Cohen *et al.*, 2015a,b). In their evaluation, the FEMA Expert Panel noted that based on the anticipated annual volume of use (700 kg), the *per capita* intake ("eaters only") of OS-GTE from use as a flavor modifier is estimated to be 103 µg/person/day (2 µg/kg body weight/day) (Cohen *et al.*, 2015a,b). Subsequently, Kemin increased the number of food categories and revised the use levels at which OS-GTE may be added to foods as a flavor modifier. The FEMA Expert Panel has evaluated these amended uses and concluded them to be GRAS. The amended conditions of uses have been updated in the latest FEMA publication of GRAS flavoring substances (Cohen *et al.*, 2017). The average usual use levels of OS-GTE as a

flavor modifier now range from 50 to 750 ppm, while the average maximum use levels range from 400 to 2,800 ppm.

The food categories to which OS-GTE is intended for addition as an antioxidant, as defined in Table 1.3-1 of this GRAS notice, are nearly identical to those for which OS-GTE is intended for use as a flavor modifier, with the exception of processed cheeses. Accordingly, the addition of OS-GTE to foods as an antioxidant will not be additive to its existing uses as a flavor modifier. In some of the food categories, the intended use levels of OS-GTE as an antioxidant are higher than those from its current uses as a flavor modifier. The estimated exposure to OS-GTE from its intended uses as an antioxidant in foods are described further in Part 3.2.

Uses of OS-GTE in Other Countries

In China, OS-GTE (referred to as "tea polyphenol palmitate", CNS 04.021) is a permitted food additive under GB:2760-2014 (Ministry of Health of the PRC, 2014). Specifically, "tea polyphenol palmitate" may be added as an antioxidant to "fats and oils essentially free from water" at levels up to 600 ppm.

3.1.3 Intake of Catechins from Green Tea

While monomeric flavan-3-ols are present in various food sources, including fruits (*e.g.*, apples, apricots, cherries, grapes, peaches, *etc*.), cocoa/chocolate, and red wine, the richest dietary source of these polyphenols is green tea (Manach *et al.*, 2004; Lotito and Frei, 2006). The USDA has compiled flavonoid composition data for various foods, including brewed green tea (Bhagwat *et al.*, 2014). Based on the mean concentration of catechins that have been reported in this database, it is estimated that 1 standard 240 mL serving of brewed green tea will provide approximately 316 mg of total catechins (Table 3.1.3-1).

Table 3.1.3-1 Estimated Intake of Catechins from the Consumption of Brewed Green Tea

Constituent	Mean Concentration in Brewed Green Tea (mg/100 mL)[a]	Intake from 1 Serving of Brewed Green Tea (mg/serving)[b]
(-)-Epicatechin (EC)	8.33	20
(-)-Epicatechin 3-gallate (ECG)	17.94	43
(-)-Epigallocatechin (EGC)	29.18	70
(-)-Epigallocatechin 3-gallate (EGCG)	70.20	168
(+)-Catechin	4.47	11
(+)-Gallocatechin	1.54	4
Total	131.66	316

[a] Data were obtained from the *USDA Database for the Flavonoid Content of Selected Foods* (Bhagwat *et al.*, 2014).
[a] 1 standard U.S. cup is approximately 8 fluid ounces or approximately 240 mL.

3.2 Estimated Intake of OS-GTE from its Intended Uses as an Antioxidant

3.2.1 Methodology

An assessment of the anticipated dietary exposure to OS-GTE under the intended conditions of use (see Table 1.3-1) was conducted using data available in the 2011-2012 cycles of the U.S. National Center for Health Statistics' (NCHS) National Health and Nutrition Examination Survey (NHANES) (CDC, 2015). In the NHANES, information on food consumption was collected from individuals *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2). In addition to collecting information on the types and quantities of foods being consumed, NHANES gathers socio-economic, physiological, and demographic information from individual participants in the survey, such as sex, age, height and weight, and

other variables useful in characterizing consumption. Sample weights were incorporated with NHANES data to compensate for the potential under-representation of intakes from specific populations and allow the data to be considered nationally representative (USDA, 2014; CDC, 2015).

Estimates for the daily intake of OS-GTE represent projected 2-day averages for each individual from Day 1 and Day 2 of the 24-hour dietary recalls collected as part of NHANES 2011-2012. These average amounts comprised the distribution from which the mean and percentile intake estimates of OS-GTE were generated. Mean and percentile estimates were generated incorporating survey weights in order to provide representative intakes for the entire U.S. population. In the exposure assessment, it was assumed that OS-GTE will be added to all food products within any given intended food use categories at the maximum use level specified in Table 1.3-1. Additionally, as mentioned in Part 1.3, OS-GTE is not intended for addition to foods for which a standard of identity exists within the U.S. regulations. Nonetheless, OS-GTE may be used in products that are similar to foods for which a standard of identity exists. Given that there is only a limited number of food codes available for the non-standardized forms of these products (*e.g*., margarine-like products), the food codes for the standardized food products were also selected as a surrogate to ensure that the consumption of these non-standardized food products have been adequately captured. For some of the food categories listed in Table 1.3-1 in which OS-GTE is intended for addition (*e.g.*, fats and oils), these may in turn be added to other processed food products (*e.g.*, baked goods). The exposure to OS-GTE from these intended food uses were accounted for by applying the intended use level (*e.g.*, 0.28%) to the relevant ingredient fraction in the final food products as consumed.

3.2.2 Estimated Intake

The estimated daily intake of OS-GTE from its intended food uses (Table 1.3-1) is summarized in Table 3.2.2-1 on an absolute basis (mg/person/day), and in Table 3.2.2-2 on a body weight basis (mg/kg body weight/day). "*Per capita*" intake refers to the estimated intake of OS-GTE averaged over all individuals surveyed, regardless of whether they potentially consumed food products containing OS-GTE, and therefore includes individuals with "zero" intakes (*i.e*., those who reported no intake of food products containing OS-GTE during the 2 survey days). "Consumer-only" intake refers to the estimated intake of OS-GTE by those individuals who reported consuming food products containing OS-GTE. Individuals were considered "consumers" if they reported consumption of 1 or more food products containing OS-GTE on either Day 1 or Day 2 of the survey. The percentage of consumers was high among all age groups evaluated in the current intake assessment; greater than 76.2% of the population groups consisted of consumers of food products in which OS-GTE is currently intended for use. Since the "consumer-only" intakes are more applicable to the assessment of safety as they are more likely to represent exposure in the target populations, only these results are considered.

Among the total population, the mean and 90th percentile consumer-only intakes of OS-GTE were determined to be 135 and 270 mg/person/day, respectively. Of the individual population groups, male adults were determined to have the greatest mean and 90th percentile consumer-only intakes of OS-GTE on an absolute basis, at 162 and 348 mg/person/day, respectively.

Table 3.2.2-1 Summary of the Estimated Daily Intake of OS-GTE from Intended Food Uses in the U.S. by Population Group (2011-2012 NHANES Data)

Population Group	Age Group (Years)	*Per Capita* Intake (mg/day)		Consumer-Only Intake (mg/day)			
		Mean	90th Percentile	%	n	Mean	90th Percentile
Infants and Young Children	0 to 2	55	138	76.2	504	72	156
Children	3 to 11	116	205	100.0	1,522	116	205
Female Teenagers	12 to 19	98	195	99.5	531	99	195
Male Teenagers	12 to 19	131	256	98.6	513	133	256
Female Adults	20 and up	126	254	99.5	2,201	127	255
Male Adults	20 and up	161	348	99.5	2,079	162	348
Total Population	All Ages	133	269	98.7	7,350	135	270

OS-GTE = Oil-Soluble Green Tea Extract; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

On a body weight basis, the mean and 90th percentile consumer-only intakes of OS-GTE among the total population were determined to be 2.3 and 5.0 mg/kg body weight/day, respectively. Among the individual population groups, infants and young children were determined to have the highest mean and 90th percentile consumer-only intake of any population group, at 5.9 and 12.2 mg/kg body weight/day, respectively.

Table 3.2.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of OS-GTE from Intended Food Uses in the U.S. by Population Group (2011-2012 NHANES Data)

Population Group	Age Group (Years)	*Per Capita* Intake (mg/kg bw/day)		Consumer-Only Intake (mg/kg bw/day)			
		Mean	90th Percentile	%	n	Mean	90th Percentile
Infants and Young Children	0 to 2	4.5	11.0	76.2	501	5.9	12.2
Children	3 to 11	4.5	8.8	100.0	1,522	4.5	8.8
Female Teenagers	12 to 19	1.8	4.0	99.5	520	1.8	4.0
Male Teenagers	12 to 19	2.0	3.7	98.6	510	2.0	3.7
Female Adults	20 and up	1.8	3.8	99.5	2,178	1.8	3.8
Male Adults	20 and up	1.9	4.1	99.5	2,060	1.9	4.1
Total Population	All Ages	2.3	5.0	98.7	7,291	2.3	5.0

bw = body weight; OS-GTE = Oil-Soluble Green Tea Extract; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

3.3 Summary

Consumption data from the 2011-2012 NHANES dataset were used to estimate the intakes to OS-GTE under its intended conditions of use as an antioxidant in foods. A number of conservative assumptions were included in the exposure assessment. For example, it was assumed that all food products within a food category contain OS-GTE at the maximum specified level of use. In reality, the levels of OS-GTE added to specific foods will vary, and it is unlikely to have 100% market penetration. In addition, short-term food consumption surveys, such as the typical 2- or 3-day dietary surveys, may overestimate the consumption of food products that are consumed relatively infrequently (Anderson, 1988; Alger *et al.*, 2013).

The resulting mean and 90th percentile intakes of OS-GTE by the total U.S. population is presented in Table 3.3-1, alongside the estimated intake of the green tea catechin component of OS-GTE. The latter was derived using the specified content of palmitoylated catechins in OS-GTE (up to 82% on an EGCG monopalmitate equivalent basis), and the estimation that the green tea catechins component accounts for approximately 57% of the total palmitoylated catechins on a weight-by-weight basis (see Part 2.1.6). The corresponding intakes among male adults, who were identified as having the highest mean and 90th percentile intakes of OS-GTE on an absolute basis, are also presented in Table 3.3-1. The 90th percentile intake of OS-GTE among male adults (348 mg/day), corresponds to intake of approximately 163 mg/day of green tea catechins, which is less than the amount of green tea catechins (approximately 316 mg) that is typically consumed from a 240 mL serving of green tea (see Table 3.1.3-1). Additionally, as explained in Part 2.1.6, approximately 30% w/w of the total palmitoylated catechins is accounted for by EGCG. Accordingly, the 90th percentile intake of OS-GTE among male adults (348 mg/day) corresponds to intake of approximately 86 mg/day of EGCG, specifically. This amount is also less than the level of EGCG (approximately 168 mg) that is typically consumed from a 240 mL serving of green tea (see Table 3.1.3-1).

While infants and young children were identified as the population group having highest estimated intake of OS-GTE on a body weight basis (mean and 90th percentile intakes of 5.9 and 12.2 mg/kg body weight/day, respectively), it should be noted that the estimates described herein assume *all* products, including those consumed by younger individuals, would contain OS-GTE at the maximum intended use levels. Moreover, OS-GTE will not be added to food products that are specifically targeted towards infants and young children (*i.e.*, infant formula and baby foods).

Table 3.3-1 Estimated Intake of OS-GTE and its Green Tea Catechins Component from its Intended Uses as an Antioxidant in Foods

Population Group	Estimated Intake of OS-GTE from its Intended Uses (mg/day)	Estimated Intake of Green Tea Catechins from the Intended Uses of OS-GTE (mg/day)[a]	Estimated Intake of EGCG from the Intended Uses of OS-GTE (mg/day)[b]
Male Adults			
Mean	162	76	40
90th Percentile	**348**	**163**	**86**
Total U.S. Population			
Mean	135	63	33
90th Percentile	270	126	66

EGCG = (-)-epigallocatechin gallate; OS-GTE = Oil-Soluble Green Tea Extract; U.S. = United States.
[a] Calculated as: (Estimated intake of OS-GTE from its intended uses) x 0.82 x 0.57
[b] Calculated as: (Estimated intake of OS-GTE from its intended uses) x 0.82 x 0.30

Part 4. §170.240 Self-Limiting Levels of Use

The bitterness and astringency of green tea aqueous infusions are primarily elicited by their catechin constituents (Wang *et al.*, 2000; Namal Senanayake, 2013). Kemin has conducted tests on the sensory properties of their OS-GTE material. The average tolerance threshold was determined as 10,000 ppm (1%) for OS-GTE. Approximately 50% of the individuals in a sensory panel reported a "dislike" to the test product (butter cookies) containing OS-GTE at this level of addition.

Accordingly, the intended uses of OS-GTE will be limited in that it will only be added to food products at levels needed to achieve its technological function (*i.e.*, as an antioxidant), without negatively impacting the organoleptic properties of foods, and thereby, consumer acceptability.

Part 5. §170.245 Experience Based on Common Use in Food Before 1958

The conclusion that the intended uses of OS-GTE as an antioxidant in foods is GRAS is made through scientific procedure, and not through experience based on common use in food before 1958. Therefore, this part is not applicable for the present GRAS notice.

Part 6. §170.250 Narrative and Safety Information

6.1 Introduction

To support the safety of OS-GTE, Kemin has conducted a comprehensive series of product-specific toxicological studies with the material; these studies are described in Part 6.3 below. The available data, which include *in vitro* hydrolysis studies conducted by Kemin and published studies on one representative form of palmitoylated catechins [*i.e.*, 3-palmitoyl-(+)-catechin], suggest that the palmitoylated catechins in OS-GTE will undergo hydrolysis to release palmitic acid and green tea catechins within the body. As explained in Part 6.2, these individual constituents are anticipated to undergo the same metabolic processes as those that would occur when they are consumed from naturally occurring dietary sources. Given that OS-GTE will be hydrolyzed to green tea catechins and palmitic acid, the safety of these constituents, when consumed under the intended conditions of use for OS-GTE, were also considered (see Part 6.5).

To identify the relevant information, comprehensive and detailed searches of the published scientific literature pertaining to the safety of OS-GTE were conducted through July 2017 using the following databases: Adis Clinical Trials Insight, AGRICOLA, AGRIS, Allied & Complementary Medicine™, BIOSIS® Toxicology, BIOSIS Previews®, CAB ABSTRACTS, Embase®, Foodline®: SCIENCE, FSTA®, MEDLINE®, NTIS: National Technical Information Service, and ToxFile®. All of the pivotal data and information used to establish the safety of OS-GTE under its intended conditions of use as an antioxidant in foods are "generally available" (*i.e.*, in the public domain), and none are exempt from disclosure under the Freedom of Information Act. A listing of the data and information discussed herein is provided in Part 7.

6.2 Absorption, Distribution, Metabolism, Elimination (ADME)

6.2.1 Palmitoylated Catechin

6.2.1.1 Available Data on OS-GTE

Kemin has conducted *in vitro* experiments to confirm that the palmitoylated catechins will be hydrolyzed into their individual palmitic acid and green tea catechin constituents under conditions that simulate gastric and intestinal environments (unpublished data). In general, fatty acid esters are subject to hydrolysis at low pH, such as those that are present within the stomach. In one experiment, OS-GTE was emulsified in simulated gastric fluid (pH 1.25) and incubated at 37°C. Samples were collected periodically to monitor the changes in the concentration of palmitic acid over time. Following 2 hours of incubation, which is considered to be representative of the transit time through the stomach, the investigators reported that approximately 10 to 20% of the palmitoylated catechins was hydrolyzed. In a second experiment, OS-GTE was incubated in a phosphate buffer (pH 7) with pancreatic carboxylester lipase (cholesterol esterase) isolated from porcine pancreas, in the presence of porcine bile extract. The reaction mixture was incubated at 37°C. Similar to the first experiment, samples were collected periodically to monitor the changes in the

concentration of palmitic acid over time. Based on the results obtained, the investigators concluded that approximately 25% of the palmitoylated catechins is hydrolyzed within 2 hours of incubation with pancreatic carboxylester lipase.

Together, these results support that palmitoylated catechins can undergo hydrolysis to their individual green tea catechin and palmitic acid constituents within the gastrointestinal tract. As discussed further in Part 6.2.1.2 below, hydrolysis of the palmitoylated catechins can also occur following absorption and uptake, upon which the released green tea catechins and palmitic acid will be metabolized in the same manner as the constituents that are consumed from naturally occurring dietary sources.

6.2.1.2 Published Data on Related Compounds

In addition to the *in vitro* hydrolysis studies conducted by Kemin, 2 studies were identified in the literature that examined the metabolic fate of 3-palmitoyl-(+)-catechin, a representative form of the palmitoylated catechins.

Ryle *et al.* (1983) reported a study where the absorption profile of 3-palmitoyl-(+)-catechin and (+)-catechin was investigated. Fasted male RAI(f) rats were administered a single dose of radiolabeled 3-palmitoyl-[U-^{14}C]-(+)-catechin or [U-^{14}C] (+)-catechin by gavage. Although statistical testing was not reported in the study, it was indicated that 3-palmitoyl-(+)-catechin reached higher peak concentrations in the liver (60.29 µg/g tissue at 7 hours following dosing) when compared to (+)-catechin (18.09 µg/g tissue at 2 hours following dosing). Moreover, the AUC_{0-24h} of compounds detected in the liver was reported as 830.58 hr•µg/g for 3-palmitoyl-(+)-catechin and 281.37 hr•µg/g for (+)-catechin. Even after considering the molar mass of 3-palmitoyl-(+)-catechin (528 g/mol) to be almost twice that of (+)-catechin (290 g/mol), the study authors suggest that based on these results, 3-palmitoyl-(+)-catechin may have higher peak concentrations and remain in the liver for longer than (+)-catechin.

The metabolic processes of 3-palmitoyl-(+)-catechin were further investigated *in vitro* and in rats by Hackett and Griffiths (1982). Incubation of 3-palmitoyl-(+)-catechin with pancreatic lipase *in vitro* did not result in any hydrolysis of the compound, and experiments reported with inverted rat intestinal sacs suggest that it is the palmitoylated compound that undergoes absorption. However, hydrolysis of 3-palmitoyl-(+)-catechin was reported following *in vitro* incubation with rat plasma and from liver perfusion studies, suggesting that hydrolysis can occur following absorption. Data obtained from experiments conducted in Wistar rats administered radiolabeled 3-palmitoyl-(+)-[U-^{14}C]-catechin by gavage is consistent with those obtained from the *in vitro* and *ex vivo* studies. Less than 5% of the administered 3-palmitoyl-(+)-catechin was recovered unchanged in the feces of these animals, and none of the parent compound was detected in the urine or bile, suggesting 3-palmitoyl-(+)-catechin is absorbed and becomes excreted predominantly as metabolites. A large proportion (63%) of the administered dose of 3-palmitoyl-(+)-catechin was recovered in the urine, mainly as the glucuronide and sulfate conjugates of (+)-catechin or 3'-O-methyl-(+)-catechin. Some of the conjugated metabolites of (+)-catechin were also excreted in the bile. Ring-scission products of (+)-catechin (*e.g.*, δ-phenyl-valerolactones and phenolic acids) were detected in the urine, suggesting that the (+)-catechin conjugates excreted through the bile were further subjected to deconjugation and cleavage by the intestinal microflora. Overall, the metabolite profile of rats administered 3-palmitoyl-(+)-catechin is consistent with those expected of green tea catechins (see Part 6.2.2). Therefore, it is expected that the catechin components that are released from palmitoylated catechins following hydrolysis will be processed in the same manner as those consumed from green tea.

6.2.2 Green Tea Catechins

Based on the results of the *in vitro* hydrolysis studies conducted with Kemin's OS-GTE, and from the studies identified on 3-palmitoyl-(+)-catechin (Hackett and Griffiths, 1982; Ryle *et al.*, 1983), it is apparent that palmitoylated catechins will undergo hydrolysis to release its individual green tea catechins. Green tea catechins are known to undergo extensive biotransformation before being excreted (Manach *et al.*, 2005; Williamson and Manach, 2005; Rein *et al.*, 2013; Qiao *et al.*, 2014). Metabolism occurs in the small intestines and liver, leading to the formation of methylated, glucuronidated, and sulfated metabolites (Manach *et al.*, 2005; Feng, 2006). Green tea catechins and their metabolites are then excreted in the urine, or alternatively, they may be transported back into the intestines *via* biliary excretion where the resident microflora can further metabolize the compounds to valerolactones and phenolic acids (Feng, 2006; Clifford *et al.*, 2013).

6.2.3 Palmitic Acid

The palmitic acid moiety obtained from the hydrolysis of OS-GTE is expected to undergo the same metabolic pathways as fatty acids that are consumed in the diet. The majority of fat digestion occurs within the small intestine (Hall, 2011). The dietary fats are emulsified by bile and digested by gastrointestinal enzymes to release free fatty acids (Ramirez *et al.*, 2001; Hall, 2011). Longer-chain fatty acids with chain lengths of 12 or more (such as palmitic acid) are too insoluble to pass directly into circulation (Poquet and Wooster, 2016; Ferreira and Tonetto, 2017; Shah and Limketkai, 2017). The released fatty acids are solubilized in bile micelles, which facilitates their uptake into the enterocyte (Linscheer and Vergroesen, 1994; Hall, 2011). Within the enterocytes, the absorbed fatty acids can be re-esterified to form new triglycerides (Ramirez *et al.*, 2001; Hall, 2011). The resulting triglycerides are then assembled into chylomicrons, which are then released into lymphatic system for distribution into systemic circulation and uptake and utilization by peripheral tissues (Hall, 2011; Poquet and Wooster, 2016).

6.3 Toxicological Studies Conducted with OS-GTE

Kemin has conducted a series of toxicological studies with OS-GTE, including genotoxicity/mutagenicity testing (bacterial reverse mutation assay, an *in vivo* mouse micronucleus assay, and a mouse sperm malformation assay), as well as a 30-day and 90-day oral toxicity study in rats. The OS-GTE test articles in these studies contained 68.41% palmitoylated catechins (expressed as EGCG monopalmitate equivalents), and they are considered representative of the commercially available OS-GTE material. These toxicological studies have been published by Liu *et al.* (2017), and they are summarized in Parts 6.3.1 to 6.3.3 below.

6.3.1 Genotoxicity/Mutagenicity

6.3.1.1 Bacterial Reverse Mutation Assay

The bacterial reverse mutation assay for OS-GTE, as reported by Liu *et al.* (2017), was conducted in accordance to the Food Safety and Toxicology Assessment Procedures and Methods (Chinese Standard GB:15193-2003) (Ministry of Health of the PRC, 2004). The assay was performed in *Salmonella typhimurium* TA97a, TA98, TA100, and TA102. OS-GTE concentrations of 8, 40, 200, 1,000, and 5,000 µg/plate were tested in triplicate, with and without S9 metabolic activation. The negative control (sterile water), solvent control (sterile dimethyl sulfoxide), and positive controls were prepared concurrently with the treatment groups. The positive controls used included 2 µg sodium azide (NaN3)/plate, 50 µg Dexon dimethylamino benzene diazonium sulfonate (fenaminosulf)/plate, 10 µg 2-acetylaminofluorene (2-AAF)/plate, and 25 µg 2-hydroxyanthraquinone (2-HA)/plate. The number of revertant colonies was manually counted.

No mutagenic responses were reported in any tester strain treated with OS-GTE in the presence or in the absence of metabolic activation. The number of revertant colonies was similar between the treatment group and the negative controls (solvent and untreated) at all tested concentrations. The number of revertant colonies in the positive control groups was at least 2-fold greater than that of the negative control group. The background lawn was unaffected at a concentration of 5,000 µg OS-GTE/plate. The results of this study suggest that OS-GTE is not mutagenic under the conditions of the assay.

6.3.1.2 In vivo Mouse Micronucleus Assay

The *in vivo* mouse micronucleus assay for OS-GTE, as reported by Liu *et al.* (2017), was conducted in accordance to the Food Safety and Toxicology Assessment Procedures and Methods (Chinese Standard GB:15193-2003) (Ministry of Health of the PRC, 2004). Animals were housed individually in stainless steel cages and acclimated to the laboratory conditions (temperature 20 to 25°C, humidity 40 to 70%) for 3 days prior to study initiation. Five male and 5 female ICR mice, weighing 25 to 28 g, were randomly assigned to 5 groups. Mice were treated by gavage (20 mL/kg) with either vegetable oil (negative control), 40 mg cyclophosphamide (positive control)/kg body weight, or OS-GTE at doses of 2.5, 5.0, or 10.0 g/kg body weight, twice within a 24-hour interval. Animals were euthanized by cervical dislocation 6 hours following administration of the second dose. The sternal bone marrow was extracted for preparation of bone marrow smears, which were fixed with methanol and stained with Giemsa. For each animal, 1,000 polychromatic erythrocytes (PCE) were counted and the incidence of micronucleated PCE and the ratio of PCE and normochromatic erythrocytes (NCE) were calculated.

The number of cells with micronucleated PCE and PCE/NCE ratio following treatment with OS-GTE were similar to the negative control group. The micronucleus frequency was similar between all groups receiving OS-GTE and the negative control. Conversely, the micronucleus frequency in both male and female animals of the positive control group was significantly higher than that of the negative control group ($p<0.01$). The results of this study suggest that OS-GTE is not clastogenic under the conditions of the assay.

6.3.1.3 Mouse Sperm Malformation Assay

The mouse sperm malformation assay for OS-GTE, as reported by Liu *et al.* (2017), was conducted in accordance to the Food Safety and Toxicology Assessment Procedures and Methods (Chinese Standard GB:15193-2003) (Ministry of Health of the PRC, 2004). Animals were housed individually in stainless steel cages and acclimated to the laboratory conditions (temperature 20 to 25°C, humidity 40 to 70%) for 3 days prior to study initiation. Twenty-five male ICR mice, weighing 25 to 30 g, were randomized into 5 groups (5 animals/group). Animals were administered OS-GTE by gavage at doses of 2.5, 5.0, or 10.0 g/kg body weight/day for 5 days and a volume of 20 mL/kg body weight. The control groups received either vegetable oil (negative control) or 1.5 mg mitomycin C (MMC) (positive control)/kg body weight. Animals were euthanized by cervical dislocation 30 days following administration of the last dose. The bilateral epididymides were removed and a filtrate smear was prepared. The filtrate smear was air dried, fixed with methanol, and stained with 1% eosin for microscopy. Under high magnification, spermatozoa with morphological abnormalities were examined and counted based on evaluation of 1,000 spermatozoa per animal for the calculation of malformation rates.

The sperm malformation rate was significantly higher in the positive control group compared to the negative control group ($p<0.01$). No significant differences in the incidence of sperm malformation were reported between animals receiving OS-GTE and the negative control group. Moreover, no significant differences were reported on the incidence of specific sperm abnormalities (*e.g.*, amorphous, no hook,

folding, fat head, banana, double head, or double tail) following administration of OS-GTE in comparison to the negative controls.

6.3.2 Short-Term (30-Day) Oral Toxicity Study

A short-term oral toxicity study has been conducted in which Sprague-Dawley rats (10/sex/group) were administered OS-GTE by gavage for 30 days (Liu *et al.*, 2017). The study was performed in accordance with the Health Food Test and Evaluation Technical Guidelines (2003) from the Chinese Ministry of Health (Ministry of Health of the PRC, 2003).

The test animals were individually caged and were acclimated to the laboratory conditions (temperature 20 to 23°C, humidity 55 to 70%) for 3 days prior to study initiation. Following the acclimatization period, 100 healthy Sprague-Dawley rats were randomized into groups (10 sex/group) to receive by gavage OS-GTE in edible vegetable oil for 30 days. The OS-GTE formulation was composed of 35% OS-GTE and 65% vegetable oil. This formulation was administered by gavage at doses of 1.67, 3.33, or 6.67 g/kg body weight/day, which corresponded to OS-GTE doses of 0.58, 1.17, and 2.33 g OS-GTE/kg body weight/day. In addition, a separate group of animals received distilled water by gavage as a negative control, and another group received edible vegetable oil as a vehicle control. The animals were allowed free access to food and water. General observations and mortality were recorded daily. Body weight, food consumption and food utilization rate were measured weekly. Upon completion of the 30-day treatment period, blood was collected from the caudal vein for measurement of standard hematological and serum biochemistry parameters. Liver, kidney, spleen, and testis/ovary were collected for gross anatomical and histopathological examination.

There were no overt signs of toxicity and no mortalities observed over the course of the 30-day study. All animals showed normal hair color, behavior, and feces and urine excretion. There were no statistically significant dose-dependent adverse effects on body weights, food intake, food utilization rate or any hematological and biochemical parameters measured, which were within the normal range for the strain and age of this strain of rat. There were no macropathological changes attributable to treatment. The organ weights, both absolute and relative to body weight, were unaffected by treatment. No abnormal histopathological changes attributable to OS-GTE were reported. One to 3 rats from both the treated and control groups exhibited mild congestion of the central hepatic vein, presence of small vacuoles in the liver cells, scattered infiltration by inflammatory cells, and isolated focal necrosis. None of these lesions were dose-dependent or were present to any greater degree in animals receiving OS-GTE in comparison to the controls. In the kidneys, spontaneous lesions were observed such as mild swelling of the tubular epithelial cells, mild vascular dilatation and hyperemia of the stroma, and mild focal infiltration of inflammatory cells in the renal cortex. However, since these observations were reported at similar frequencies (1 or 2/group) in the animals receiving OS-GTE and the controls (both vehicle and water), they were not considered to be toxicologically relevant. No lesions were reported in the stomach, intestines, testes, or ovaries in any of the animals.

The no-observed-adverse-effect level (NOAEL) was concluded by the study authors to be 2.33 g OS-GTE/kg body weight/day, the highest dose tested.

6.3.3 Sub-Chronic (90-Day) Oral Toxicity Study

A sub-chronic oral toxicity study was conducted where Sprague-Dawley rats received OS-GTE as a dietary admixture for 90 days (Liu *et al.*, 2017). The study was performed in accordance with the Food Safety Toxicology Assessment Procedures and Methods (GB:15193-2003) (Ministry of Health of the PRC, 2004).

The test animals were housed individually in stainless steel cages and acclimated to the laboratory conditions (temperature 20 to 25°C, humidity 40 to 70%) for 3 days prior to study initiation. Following the acclimatization period, 80 healthy, weaned Sprague-Dawley rats (10/sex/group) weighing approximately 60 to 80 g [initial weight (mean±SD) of 75.6±4.1 g in females and 74.9±6.8 g in males] were randomized into groups to receive OS-GTE at concentrations of 0 (control), 1.56, 3.12, or 6.25 g/kg diet for 90 days. These dietary concentrations were estimated to provide 0 (control), 125, 250, or 500 mg/kg body weight/day of OS-GTE, based on the assumption that the daily amount of feed consumed by the rat is equivalent to approximately 8% of their body weight (TERA, 2017). The animals were allowed free access to food and water. General observations and mortality were recorded daily. Body weight, food consumption and food utilization rate were measured weekly. Following an overnight fast, blood samples were collected from the tip of the tail for assessment of hematology and serum biochemistry parameters during Week 7 and at the end of the study. At study termination, the liver, kidney, spleen, and testes were collected, examined, and weighed, and the organ-to-body weight ratios (relative organ weight) were calculated. Liver, kidney, spleen stomach, duodenum, testes, and ovaries were embedded in paraffin, stained with hematoxylin and eosin, and examined for histopathological changes.

There were no overt signs of toxicity and no deaths. There were no statistically significant, dose-dependent adverse effects in body weights, food intake, food utilization rate, and hematological and biochemical parameters measured at Week 7 and at the end of the study. All of these values were within the normal reference range for this strain and age of rat. There were no statistically significant, dose-dependent adverse effects in the absolute and relative organ weights of the liver, kidney, spleen, and testis. No macropathological or histopathological abnormalities were observed that were attributable to treatment with OS-GTE. Mild hyperemia of the hepatic central vein was reported in 2/10 female control animals and granular-like ballooning degeneration was reported in hepatocytes of 1/10 male animal of the control group. No corresponding effect was reported in male or female animals receiving the highest dose of OS-GTE. Significantly reduced spermatogenic epithelial cells of seminiferous tubules were reported in 1/10 male control animal. Interstitial capillary congestion in the kidneys was reported in 4/10 female control and 1/10 high-dose male and female. No abnormal findings were observed in the spleen, ovaries, stomach, and intestines.

The NOAEL was concluded by the study authors to be 500 mg OS-GTE/kg body weight/day, the highest dose tested, based on the dietary inclusion rate of 6.25 g OS-GTE/kg feed.

6.4 Other Data on Palmitoylated Catechins

6.4.1 Preclinical Studies Conducted with OS-GTE

In addition to the published toxicological studies that have been conducted with OS-GTE (Liu *et al.*, 2017), there have been acute oral toxicity studies, as well as one repeated-dose study in dogs, that have been conducted with the material (unpublished data). As these studies provide only limited information, they are considered to be only corroborative, and not pivotal, in supporting the safety of OS-GTE for its intended uses as an antioxidant in foods.

The oral median lethal dose (LD_{50}) of OS-GTE, when administered by gavage, has been concluded to be greater than 20.0 g OS-GTE/kg body weight in Sprague-Dawley rats (10/sex) and ICR mice (10/sex). These studies were performed according to the Food Safety Toxicology Assessment Procedures and Methods (Chinese Standard GB:15193-2003) (Ministry of Health of the PRC, 2004). OS-GTE was administered after a 16-hour fasting period as 2 separate doses (10 g/kg body weight each), with a 6-hour interval in between

the dosing periods. The animals were monitored for 2 weeks after administration of the test article. No overt signs of toxicity were reported and there were no deaths.

A study has been conducted where healthy Beagle dogs (5/sex/group) were fed diets containing OS-GTE at concentrations corresponding to theoretical doses of 0, 10, 20, or 50 mg/kg body weight/day for 84 days. However, this study was not designed to assess the safety of OS-GTE, and only limited toxicological endpoints were assessed. For instance, the animals were not terminated at the end of the study period, and thus, were not subjected to macroscopic and histopathological examinations. Statistical analyses were also not conducted on the data collected. Nevertheless, all the dogs were generally reported to be in good health, except for 1 dog in the high-dose group that developed hind limb paralysis on Day 31 and had to be euthanized on Day 33. Upon necropsy, spinal cord mass, cartilaginous mass with spinal cord compression and axonal degeneration, was reported in this animal, though this finding was determined by the investigators to be unrelated to OS-GTE**.** None of the other animals exhibited any signs of overt toxicity during the study. No notable treatment-related changes in body weight or food consumption were observed throughout the duration of the study, and no changes in the stool consistency were reported. Blood and urine samples were collected from the animals on Days 0, 28, 56, and 84. The hematology, serum chemistry, and urinalysis parameters were within the normal reference ranges and did not appear to be altered in a dose-dependent manner. Overall, the results of this study suggest that inclusion of OS-GTE in the diet of dogs for 84 days, at concentrations providing up to 50 mg OS-GTE/kg body weight/day, did not result in any adverse effects in the animals.

6.4.2 Clinical Data on 3-Palmitoyl-(+)-Catechin

Clinical studies with OS-GTE have not been conducted. However, the literature search identified one study that examined the efficacy of orally administered 3-palmitoyl-(+)-catechin on liver health and function in patients with alcoholic liver disease (World *et al.*, 1987). In this prospective, randomized, double-blind, placebo-controlled study, 33 individuals with biopsy-confirmed alcoholic liver disease were allocated to receive either 3-palmitoyl-(+)-catechin at a dose of 1,500 mg/day (taken as 500 mg capsules 3 times daily) or a placebo capsule for 3 months. The participants were selected from patients with chronic alcoholism who were admitted to the clinic for detoxification treatment.

Three of the participants in the placebo group were lost to follow-up; accordingly, 14 participants in the placebo group and 16 participants in the 3-palmitoyl-(+)-catechin group completed the study. Overall, no statistically significant differences in the mean liver biopsy scores, lipid content in the liver, or hepatic clearance rates of indocyanine green were reported between the active or placebo group in the beginning and end of the study. The results of liver function tests (as indicated by serum biochemistry parameters) were also not statistically significant between the groups at any point of the study. No adverse side effects that could be attributable to the administration of 3-palmitoyl-(+)-catechin were reported. Although this study was conducted among individuals with alcoholic liver disease, the results suggest that administration of 3-palmitoyl-(+)-catechin at doses up to 1,500 mg/day was well tolerated, with no changes to liver function observed.

6.5 Safety of the Palmitic Acid and Green Tea Catechin Components of OS-GTE

6.5.1 Safety of Palmitic Acid from the Intake of OS-GTE

Palmitic acid is a naturally occurring 16 carbon straight-chain saturated fatty acid. Saturated fatty acids including palmitic acid can be synthesized to a limited extent by the human body (IOM, 2005; Nelson and Cox, 2005). Saturated fatty acids are also present in a wide variety of animal- and plant-derived foods;

dietary sources that are particularly rich in palmitic acid include meat and dairy products, as well as palm oil (IOM, 2005; EFSA, 2010). According to data collected from the 2013-2014 cycle of the NHANES, the mean intake of saturated fats from dietary sources among individuals age 2 and older is reported at 26 g/person/day (USDA, 2016). The mean intake of palmitic acid (C16:0) specifically, among individuals age 2 and older, is reported at 14 g/person/day (USDA, 2016).

Considering that the highest level of OS-GTE intake was estimated at 348 mg/day for male adults, the amount of palmitic acid contributed by OS-GTE is considerably less than the existing dietary intake of palmitic acid among the U.S. population (*i.e.*, 14 g/person/day for individuals age 2 and older) (USDA, 2016). As such, the intake of palmitic acid from the intended uses of OS-GTE as an antioxidant in foods is not expected to pose any adverse nutritional or safety concerns.

6.5.2 Safety of Green Tea Catechins from the Intake of OS-GTE

Tea is one of the most widely consumed beverages in the world, second only to water (Technical Resources International, 2000). Despite the long history of safe consumption of green tea, the safety of green tea catechins, particularly EGCG, has been extensively scrutinized due to concerns that have arisen over their potential for mediating liver toxicity.

The effects of green tea extracts have been investigated in a number of animal studies, including comprehensive testing that were conducted by the U.S. National Toxicology Program (NTP) (NTP, 2016). While the NTP concluded that there were "no evidence of carcinogenic activity" for green tea extract in Wistar Han rats or B6C3F1/N mice, gavage administration of green tea extract was associated with various non-neoplastic lesions, including those in the liver (Chan *et al.*, 2010; NTP, 2016). Evidence of liver toxicity from green tea catechins/EGCG have also been reported in other studies (*e.g.*, Yamane *et al.*, 1996; Sakamoto *et al.*, 2001; Bun *et al.,* 2006; Isbrucker *et al.*, 2006; Chengelis *et al.*, 2008; Takami *et al.*, 2008; Kapetanovic *et al.*, 2009; Morita *et al.*, 2009; Chan *et al.*, 2010; Wang *et al.*, 2010, 2012; Saleh *et al.*, 2013; NTP, 2016; Ramachandran *et al.,* 2016). These effects may be more pronounced when administration takes place in fasted *versus* fed animals. Isbrucker *et al.* (2006) reported an approximately 10-fold reduction in the NOAEL of an EGCG preparation, from 459 mg EGCG/kg body weight/day to 40 mg EGCG/kg body weight/day, when it is administered to Beagle dogs under a fed *versus* fasted state. It has been suggested that the increased susceptibility to toxicity may be attributable to the increased bioavailability of green tea catechins, which may be modulated by the concomitant intake of food (Chow *et al.*, 2005; Isbrucker *et al.*, 2006; Kapetanovic *et al.*, 2009; Naumovski *et al*., 2015). A 2- to >4-fold increase in the area-under-the-curve has been reported when green tea catechins were administered under fasting conditions in animals (Isbrucker *et al.*, 2006; Kapetanovic *et al.*, 2009) and humans (Chow *et al.*, 2005; Naumovski *et al*., 2015).

Cases of hepatotoxicity have also been reported following the consumption of dietary supplements containing green tea extracts; these have been reviewed extensively by several authors (Sarma *et al.*, 2008; Mazzanti *et al.*, 2009, 2015; Teschke *et al.*, 2014; García-Cortés *et al.*, 2016; Brown, 2017; Yates *et al.*, 2017). Due to the nature of case reports, however, it is difficult to establish causality since the adverse effects could potentially be attributed to other factors unrelated to the use of the green tea-containing supplements. For example, many of the cases resulted from the use of multi-component supplement products containing other ingredients in addition to green tea extracts. Other possible confounders include the concomitant use of alcohol and medications, presence of pre-existing liver diseases or other medical conditions, and the possibility that undisclosed adulterants were present in the product. Additionally, in many of the case reports, precise estimates on the amount of green tea catechins consumed are not available given that only limited details on the composition of the products consumed are generally collected (*e.g.*, solvent used to obtain the green tea extract, or the content of the specific catechins). Even

so, Yates *et al.* (2017) noted that although no dose-response information could be derived from such case reports (particularly with respect to the levels of EGCG intake), the average incidence rate for hepatotoxicity was determined to be 0.00365/10,000 based on information collected over the past 10 years, which the study authors noted to be extremely rare.

To better understand the relationship between green tea preparations and liver-related adverse events in humans, Isomura *et al.* (2016) conducted a systematic review of the published literature to identify whether such effects have been consistently observed in randomized, controlled clinical trials. Liver-related adverse events were reported in 4 of the 34 studies evaluated, though none of these were considered to be serious adverse events. Across these studies, liver-related adverse events were reported in only 7 of the 1,405 individuals receiving green tea preparations (0.5%) and in 1 of the 1,200 individuals receiving the control (0.1%). Several limitations of this were recognized; for example, only studies published in English were included, the studies reviewed were largely intended to address efficacy and not safety/tolerability, and the median duration of the intervention period across the studies was relative short, being only 12 weeks. Nonetheless, the authors concluded that the "*results of the review, although not conclusive, suggest that liver-related adverse events after intake of green tea extracts are expected to be rare*". Other recent reviews have also examined the occurrence of hepatotoxicity from human intervention studies where green tea preparations were administered (Dekant *et al.*, 2017; Yates *et al.*, 2017). These authors concluded that no adverse liver effects were reported in clinical studies where EGCG was administered at doses below 600 mg/day. From this, a tolerable upper limit (UL) for EGCG was derived at 300 mg/day under the fed state, after applying an uncertainty factor of 2. At doses of EGCG that were >600 mg/day, statistically significant increases in elevated liver enzymes were observed in comparison to either the placebo control group or baseline, though these values still remained within normal ranges. The study authors also recognized that the proposed UL for EGCG may not be appropriate for traditionally prepared green tea beverages, given these have a long history of safe consumption, with no adverse health effects documented even among populations where upwards of 10 cups of green tea are consumed on a daily basis (Dekant *et al.*, 2017; Yates *et al.*, 2017).

Overall, while there is evidence to suggest that green tea catechins may be associated with liver toxicity in animal studies, these effects were generally observed following administration of large doses of green tea extracts or purified EGCG as a single bolus. Rare cases of idiosyncratic hepatotoxicity have been associated with green tea extracts in humans; even so, green tea itself is known to have a long history of safe consumption. The catechin component contributed by the intended uses of OS-GTE is well within the ranges that would be typically consumed from 1 cup of green tea. As described in Part 3.1.3, the intake of catechins from a standard 240 mL serving of brewed green tea is estimated at 316 mg. For comparison, the highest estimated daily intake of OS-GTE from its intended uses as an antioxidant in foods is estimated at 348 mg/day among male adults. This level of intake corresponds to approximately 285 mg/day of palmitoylated catechins, considering that OS-GTE is specified to contain up to 82% palmitoylated catechins (expressed as EGCG monopalmitate equivalents). Since the green tea catechins component accounts for approximately 57% of the palmitoylated catechins on a weight-by-weight basis (see Part 2.1.6), the intake of green tea catechins from OS-GTE among male adults is estimated at 163 mg/day (see Table 3.3-1). The intake of EGCG specifically, from its presence as mono-, di-, and tri-palmitates in OS-GTE, is estimated at 86 mg/day among male adults (see Table 3.3-1). This amount is also well within the level of EGCG (approximately 168 mg) that is typically consumed from a standard 240 mL serving of green tea, and the UL of 300 mg/day that have been established for EGCG based on human intervention studies (Dekant *et al.*, 2017; Yates *et al.*, 2017). Furthermore, in contrast to supplement products, which provide concentrated amounts of green tea extracts in set dosage forms, OS-GTE will be added to food products at only low levels (*i.e.*, 0.05 to 0.28%) under its intended conditions of use as an antioxidant. Moreover, since OS-GTE is intended for addition to food products, exposure will occur under a non-fasted state.

6.6 Summary of the Dataset to Support Safety

Experiments conducted *in vitro* suggest that the palmitoylated catechins in OS-GTE is subject to hydrolysis under the acidic conditions of the stomach, and by the action of pancreatic lipases in the small intestines. Additional data were identified in the literature on the metabolic fate of one representative form of palmitoylated catechins, namely 3-palmitoyl-(+)-catechin. In rats, orally administered 3-palmitoyl-(+)-catechin is extensively hydrolyzed to its (+)-catechin and palmitate constituents following absorption (Hackett and Griffiths, 1982; Ryle *et al.*, 1983). The liberated (+)-catechin is then processed in the same manner as other green tea catechins, undergoing biotransformation (*i.e.*, methylation, glucuronidation, and sulfation) and excretion in the urine, though a proportion of the metabolites can be excreted in the bile and become further degraded by the intestinal microflora (Hackett and Griffiths, 1982). The palmitic acid moiety obtained from the ingestion and subsequent hydrolysis of OS-GTE is also expected to undergo the same metabolic pathways as fatty acids that are consumed in the diet.

The safety of OS-GTE is supported by a series of preclinical toxicity studies that have been conducted with the material. OS-GTE is not mutagenic/genotoxic when tested using the Ames test, the *in vivo* mouse bone marrow micronucleus assay, and the mouse sperm malformation assay (Liu *et al.*, 2017). No consistent, statistically significant, dose-dependent adverse effects on body weight, food intake, food utilization, hematology and serum biochemistry parameters, and macroscopic and histopathological examination were reported in repeated-dose studies conducted with OS-GTE. The NOAEL in a 90-day feeding study conducted in Sprague-Dawley rats, was 500 mg OS-GTE/kg body weight/day, the highest dose tested (Liu *et al.*, 2017). The NOAEL in a 30-day gavage study conducted in Sprague-Dawley was 2.33 g/kg body weight/day, the highest dose tested (Liu *et al.*, 2017).

As the palmitoylated catechins in OS-GTE will undergo hydrolysis following consumption, the safety of its individual components (*i.e.*, green tea catechins and palmitic acid) under the intended conditions of use was also considered. The intake of palmitic acid from the intended uses of OS-GTE (*i.e.*, 90th percentile intake of 348 mg/day in adult males) is expected to be minimal in comparison to the intake of palmitic acid from dietary sources, which has been reported at 14 g/person/day in the U.S. (USDA, 2016). While there is some evidence to suggest that green tea catechins, particularly EGCG, may be associated with liver toxicity, green tea itself when consumed as its traditional preparation (*i.e.*, hot aqueous infusion) has a long history of safe consumption. The highest estimated daily intake of OS-GTE from its intended uses (*i.e.*, 348 mg/day among male adults), which is estimated to contribute approximately 163 mg/day of green tea catechins and 86 mg/day of EGCG specifically, is well within the ranges of these compounds that would be consumed from a serving of green tea (*i.e.*, 316 mg green tea catechins per 240 mL serving of brewed green tea, of which 168 mg is EGCG). The exposure to OS-GTE will occur from its inclusion as a component of foods (*i.e.*, not in a fasted state).

While there is the possibility that the bioavailability of the palmitoylated catechins in OS-GTE may be enhanced due to their greater lipophilicity in comparison to free catechin forms consumed from brewed green tea, the safety of OS-GTE itself is also supported by the results of product-specific oral toxicity studies that have been conducted in animals. No evidence of liver toxicity or other adverse effects have been observed in these studies. There is a 100-fold safety margin between the NOAEL derived from the 90-day oral toxicity study in rats (*i.e.*, 500 mg/kg body weight/day, the highest dose tested) and the estimated daily intake of OS-GTE from its intended uses in foods (*i.e.*, 90th percentile intake of 5.0 mg/kg body weight/day in the total population). These intakes estimates are considered to be “worst-case” given that several conservative assumptions are made as part of the assessment (*e.g.*, all food products within a food category contain OS-GTE at the maximum specified level of use), and they likely are an overestimation of the exposure that would occur in reality. It is also worth noting that the NOAEL of 500 mg/kg body weight/day

was the highest dose tested in the 90-day oral toxicity study conducted in rats (Liu *et al.*, 2017), suggesting the "true" NOAEL for OS-GTE may actually be higher. This is supported by the fact that no adverse effects were observed in the 30-day oral toxicity study in which OS-GTE was administered by gavage at doses of up to 2.33 g/kg body weight/day in rats (Liu *et al.*, 2017).

6.7 Expert Panel Evaluation

A Panel of Experts (the Expert Panel) who are qualified by scientific training and experience to evaluate the safety of food has unanimously concluded on the GRAS status of OS-GTE under the conditions of its intended use as an antioxidant. The Expert Panel consisted of the following qualified scientific experts: Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine); Robert J. Nicolosi, Ph.D. (University of Massachusetts Lowell); and John A. Thomas, Ph.D. (Indiana University School of Medicine)[5]. The Expert Panel was selected and convened in accordance with the FDA's guidance for industry on *Best Practices for Convening a GRAS Panel* (U.S. FDA, 2017b). Kemin ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety and toxicology. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel; no such conflicts of interest or "appearance issues" were identified. The Expert Panel received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel were not contingent upon the outcome of their deliberations.

The Expert Panel convened by Kemin independently and critically evaluated all data and information presented herein and concluded that OS-GTE, meeting appropriate food-grade specifications and manufactured consistent with cGMP, is safe and suitable for use as an antioxidant in foods as specified in Part 1.3. The Expert Panel concluded the intended uses of OS-GTE to be GRAS based on scientific procedures, and it is believed that other qualified experts would concur with these conclusions.

6.8 Conclusions

Based on the data and information presented herein, Kemin has concluded that the intended uses of their OS-GTE as an antioxidant in foods, as described in Part 1.3, are GRAS based on scientific procedures. Kemin is not aware of any data and information that are, or may appear to be, inconsistent with this conclusion. The GRAS status of OS-GTE is further supported by the unanimous consensus rendered by an independent panel of experts, qualified by experience and scientific training to evaluate the safety of food, who concluded that the intended uses of OS-GTE described herein is GRAS. OS-GTE may therefore be marketed and sold for its intended purpose in the U.S., without the promulgation of a food additive regulation under Title 21 of the CFR.

[5] The panelists participated in their individual capacities. Institutional affiliations are provided for identification purposes only.

Part 7. §170.255 List of Supporting Data and Information

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Part	Section §	Section Title
109—Unavoidable contaminants in food for human consumption and food-packaging material	109.30	Tolerances for polychlorinated biphenyls (PCB's)
170—Food additives	170.3	Definitions
	170.30	Eligibility for classification as generally recognized as safe (GRAS)

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May 31, 2018

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Dear Dr. Kolanos,

Re: GRAS Notice for Palmitoylated Green Tea Catechins (GRN No. 000772)

As requested, we are responding to your questions concerning the referenced GRAS Notice, which we received on May 24, 2018. We would like to thank the Agency for the opportunity to provide responses to these queries.

FDA's Question 1: On pp. 10–11, in the description of the manufacturing process you state that the concentrated extract of green tea catechins is reacted with a source of palmitic acid in the presence of catalyst. Please specify the source(s) of palmitic acid and identify the type of catalyst used in the reaction.

Notifier's Response: The source of highly purified palmitic acid (minimum 98% assay) used in the production of PGTC is purchased and meets food-grade specifications. The green tea catechins are reacted with the source of palmitic acid in the presence of a food-grade metal catalyst, following which the catalyst is removed by filtration, and a series of washing and purification steps are applied. Kemin routinely conducts analysis on batches of the PGTC to ensure that the levels of the residual catalyst remain within acceptable limits.

FDA's Question 2: Please clarify whether the final product, PGTC, contains unreacted palmitic acid. If it does, please provide the limit for palmitic acid, data supporting this limit, and the analytical method used to test for it.

Notifier's Response: As indicated in Part 2.1.6 of the GRAS notice (pg. 8), PGTC contains approximately 11 to 15% w/w of free palmitic acid. Table 2.1.6-1 includes analytical data conducted on 3 non-consecutive batches of PGTC demonstrating that the levels of palmitic acid fall within this range (11.08 to 13.74% w/w). The palmitic acid is assayed by an HPLC-ELSD method. As discussed in Part 6.5.1 of the GRAS notice (pg. 26 to 27), the intake of palmitic acid from the intended uses of PGTC will contribute only minimally to its intake from dietary sources.

FDA's Question 3: On p. 11 in Table 2.3.1-1, you provide specifications for PGTC. We note that the limits add to approximately 76–92% PGTC content. Please provide information regarding the remaining 8–24% PGTC content and explain why it would not be a safety concern.

Notifier's Response: As explained in Part 2.1.6 of the GRAS notice (pg. 8), PGTC is largely composed of palmitoylated catechins (66 to 82%, expressed as EGCG monopalmitate equivalents). The remainder of the

PGTC material is mainly accounted for by free palmitic acid (approximately 11 to 15% w/w), small amounts of free catechins, gallic acid, and alkaloids (caffeine, theobromine, and theophylline) which is less than 2% w/w combined, as well as proximates (ash, moisture, proteins, *etc.*) which is present at approximately 4 to 6% w/w. The sum of these parameters characterizes the composition of the PGTC to nearly 100% (85 to 105%).

It is worth reiterating that the specification limit for palmitoylated catechins (66 to 82%) is not an exact quantification of the total palmitoylated catechins present in PGTC, but rather, it is the content expressed as EGCG monopalmitate equivalents. As explained in Part 2.1.6 of the GRAS notice (pg. 8), the quantification of every individual form of the palmitoylated catechins in PGTC is not feasible by current chromatography methods. Instead, Kemin has developed a validated spectrophotometric assay to approximate the content of palmitoylated catechins present in PGTC. The content of palmitoylated catechins assessed by this method is expressed as EGCG monopalmitate equivalents, since this is the most representative species of palmitoylated catechins within the PGTC mixture (see Table 2.1.6-2).

Even though quantification of palmitoylated catechins in PGTC cannot be expressed on an absolute basis, the safety of the PGTC has been demonstrated by a series of product-specific toxicological studies that were conducted using test articles produced by the same manufacturing method and comprising the same composition as the commercially available PGTC material (Liu *et al.*, 2017). No evidence of genotoxicity/mutagenicity was observed in the bacterial reverse mutation assay, *in vivo* mouse micronucleus assay, and mouse sperm malformation assay conducted with PGTC. Moreover, the No-Observed-Adverse-Effect Level (NOAEL) was concluded to be the highest dose tested in the repeated-dose oral toxicity studies (*i.e.*, a 30-day gavage study and a 90-day feeding study) conducted with PGTC in rats. Accordingly, as discussed in Part 6 of the GRAS notice, the PGTC material produced by Kemin, which is primarily composed of palmitoylated catechins (66 to 82% expressed as EGCG monopalmitate equivalents) and free palmitic acid (approximately 11 to 15% w/w), along with small amounts of moisture, ash, and other residual components from green tea (*e.g.*, alkaloids such as caffeine, theobromine, and theophylline, and unreacted catechins and gallic acid), do not pose any safety concerns under its intended conditions of use.

FDA's Question 4: On p. 11 in Table 2.3.1-1, you list an internal spectrophotometric method as the method used to quantify palmitoylated catechins. Please provide information on whether this method has been validated.

Notifier's Response: The spectrophotometric method used to quantify the palmitoylated catechins was developed and validated by Kemin. The working range was established, and method was determined to have acceptable within-day and between-day precision.

We hope that the information provided herein is sufficient and clarifies the questions raised.

Yours sincerely,

(b) (6)

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September 28, 2018

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Dear Dr. Kolanos,

Re: GRAS Notice for Palmitoylated Green Tea Catechins (GRN No. 000772)

In an email dated August 15, 2018, the Agency noted that an Expert Panel had been convened by Kemin to evaluate the GRAS status of palmitoylated green tea catechins (OS-GTE), and accordingly, it was requested that a copy of the Expert Panel report be provided. The Agency also requested for Kemin to clarify whether the Expert Panel had access to any non-public, safety related data and information, and if so, explain how there could be a basis for a conclusion of GRAS status if qualified experts generally do not have access to this data and information.

Following the discussions that took place with the Agency *via* teleconference on September 17, 2018, we would like to revise Part 1.4, Part 6.7, and Part 6.8 of the GRAS notice as follows.

1.4 Basis for GRAS

Pursuant to § 170.30 (a) and (b) in Title 21 of the CFR (U.S. FDA, 2017a), Kemin's Oil-Soluble Green Tea Extract has been concluded to have GRAS status for use as an antioxidant in specified conventional food products, as described in Part 1.3 of this notice, on the basis of scientific procedures.

As detailed in Part 6, all of the pivotal data and information used to establish the safety of OS-GTE under its intended conditions of use as an antioxidant in foods are "generally available" (*i.e.,* in the public domain). All of the pivotal toxicological data used to support the safety of OS-GTE have been published by Liu *et al.* (2017), and these studies were conducted on the article of commerce. An Expert Panel reviewed proprietary manufacturing information that is not presented within the

notice, specifically, information regarding the identity of the catalyst and processing aids. These materials are commonly used in food production and are recognized as such by the Expert Panel. Taking into account too that the published safety studies were conducted using OS-GTE manufactured using the same processes as those employed to produce the article of commerce, all of the data and information used to support the conclusion that OS-GTE is GRAS under its intended conditions of use are considered to be publicly available.

6.7 Expert Panel Evaluation

A Panel of Experts (the Expert Panel) who are qualified by scientific training and experience to evaluate the safety of food has unanimously concluded on the GRAS status of OS-GTE under the conditions of its intended use as an antioxidant. The Expert Panel consisted of the following qualified scientific experts: Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine); Robert J. Nicolosi, Ph.D. (University of Massachusetts Lowell); and John A. Thomas, Ph.D. (Indiana University School of Medicine)[5]. The Expert Panel was selected and convened in accordance with the FDA's guidance for industry on *Best Practices for Convening a GRAS Panel* (U.S. FDA, 2017b). Kemin ensured that all reasonable efforts were made to identify and select a balanced Expert Panel with expertise in food safety and toxicology. Efforts were placed on identifying conflicts of interest or relevant "appearance issues" that could potentially bias the outcome of the deliberations of the Expert Panel; no such conflicts of interest or "appearance issues" were identified. The Expert Panel received a reasonable honorarium as compensation for their time; the honoraria provided to the Expert Panel were not contingent upon the outcome of their deliberations.

The Expert Panel convened by Kemin independently and critically evaluated all data and information presented and concluded that OS-GTE, meeting appropriate food-grade specifications and manufactured consistent with cGMP, is safe and suitable for use as an antioxidant in foods as specified in Part 1.3. The Expert Panel did review details of the manufacturing process for OS-GTE that Kemin considers to be proprietary information, namely, the identity of the catalyst and processing aids used in the production of OS-GTE. These materials are commonly used in food production and were recognized as such by the Expert Panel. Therefore, OS-GTE is concluded as GRAS under its intended conditions of use based on the published safety studies which were conducted using the article of commerce, and the fact that the product is manufactured using materials commonly employed in food ingredient production. The Expert Panel concluded the intended uses of OS-GTE to be GRAS based on scientific procedures, and it is believed that other qualified experts would concur with these conclusions.

6.8 Conclusions

Based on the data and information presented herein, Kemin has concluded that the intended uses of their OS-GTE as an antioxidant in foods, as described in Part 1.3, are GRAS based on scientific procedures. Kemin is not aware of any data and information that are, or may appear to be, inconsistent with this conclusion. The GRAS status of OS-GTE is further supported by the unanimous consensus rendered by an independent panel of experts, qualified by experience and scientific training to evaluate the safety of food, who concluded that the intended uses of OS-GTE is GRAS. OS-GTE may therefore be marketed and sold for its intended purpose in the U.S., without the promulgation of a food additive regulation under Title 21 of the CFR.

We would like to thank the Agency for the opportunity to provide responses to their queries. We hope that the information provided herein is sufficient and clarifies the questions raised.

Yours sincerely,

(b) (6)

Sylvia A. Bergman, Ph.D.
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies

GRAS Notice for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate)

Part 1. §170.225 Signed Statements and Certification

In accordance with 21 CFR §170 Subpart E consisting of §170.203 through 170.285, Kemin Industries, Inc. (d/b/a Kemin Food Technologies and referred to hereafter as "Kemin") hereby submits a Generally Recognized as Safe (GRAS) notice to the United States (U.S.) Food and Drug Administration (FDA) for Oil-Soluble Green Tea Extract (Green Tea Catechin Palmitate). It is Kemin's view that Oil-Soluble Green Tea Extract is not subject to the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act, on the basis of their conclusion that Oil-Soluble Green Tea Extract is GRAS under its intended conditions of use. In addition, as a responsible official of Kemin, I hereby certify that all data and information presented in this notice constitute a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to Kemin and pertinent to the evaluation of the safety and GRAS status of palmitoylated green tea catechins for addition to foods, as described herein.

Signed,

(b) (6)

October 2, 2018

Sylvia A. Bergman, Ph.D.
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies

Date

1.1 Name and Address of Notifier

Sylvia A. Bergman, Ph.D.
Regulatory Affairs Director
Kemin Industries, Inc. d/b/a Food Technologies
2100 Maury Street
Des Moines, IA
50317 USA

1.2 Common Name of Notified Substance

Oil-Soluble Green Tea Extract (abbreviated as OS-GTE). OS-GTE is also known by the following synonyms: Lipid-Soluble Green Tea Extract, Green Tea Catechin Palmitate, Oil-Soluble Tea Polyphenol, Palmitic Ester of Green Tea Extract, Green Tea Extract (OS), Green Tea Extract.

1.3 Conditions of Use

Oil-Soluble Green Tea Extract (OS-GTE) has been shown to be efficacious as lipophilic antioxidant in foods, and accordingly it may be used to maintain the stability and shelf-life of fat-containing foods (Patent WO 2013036934 A1 – Cutler *et al.*, 2013).

The intended food uses and use levels of OS-GTE as an antioxidant in foods are listed below in Table 1.3-1. OS-GTE is intended for addition to a variety of conventional foods in the U.S. at use levels ranging from 0.05 to 0.28% (500 to 2,800 ppm). Of note, Kemin does not intend to market OS-GTE as an antioxidant in meat and poultry products that are subject to regulation by the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA), or to foods that are promoted specifically towards infants and young children. Additionally, some of the foods listed in Table 1.3-1 have a standard of identity within Title 21 of the Code of Federal Regulations (CFR). OS-GTE is not intended for addition to standardized foods, unless it is allowed for by the applicable standard of identity.

Table 1.3-1 Intended Food Uses and Use Levels for OS-GTE in the U.S.

Food Category (21 CFR §170.3 – U.S. FDA, 2017a)	Intended Food Uses[a]	Maximum Intended Use Level of OS-GTE in Foods (%)
Baked Goods and Baking Mixes	Biscuits	0.05
	Cookies	0.05
	Crackers	0.05
	Pizza Crust	0.05
Breakfast Cereals	Instant and Regular Hot Breakfast Cereals	0.10
	Ready-to-Eat Breakfast Cereals	0.20
Cheeses	Processed Cheese	0.10
Confections and Frostings	Frosting, Icings, and Coatings	0.05
Dairy Product Analogs	Coffee Whiteners	0.05
Fats and Oils	Butter	0.28
	Fat-Based Sauces	0.28
	Margarine[b] and Margarine-like Spreads	0.28
	Mayonnaise[b] and Mayonnaise-Type Dressings	0.05
	Oils	0.28
	Salad Dressings[b]	0.10
Grain Products and Pastas	Cereal and Granola Bars	0.15
	Energy Bars, Meal Replacement Bars, and Fortified Bars	0.15
	Noodle Products	0.05
Herbs, Seeds, Spices, Seasonings, Blends, Extracts, and Flavorings	Spices, Seasonings, and Blends	0.28
Nut and Nut Products	Nut Spreads	0.10
	Processed Whole Nuts, Coated Nuts, and Mixtures	0.28
Snack Foods	Snack Foods	0.10
Soft Candy	Chocolate Confectionary	0.05

CFR = Code of Federal Regulations; OS-GTE = Oil-Soluble Green Tea Extract; U.S. FDA = United States Food and Drug Administration; U.S. = United States.

[a] OS-GTE is not intended for use in meat and poultry products that are regulated by the FSIS of the USDA.

[b] These foods have a standard of identity within Title 21 of the CFR. OS-GTE is not intended for addition to standardized foods unless permitted by the regulations.

1.4 Basis for GRAS

Pursuant to § 170.30 (a) and (b) in Title 21 of the CFR (U.S. FDA, 2017a), Kemin's Oil-Soluble Green Tea Extract has been concluded to have GRAS status for use as an antioxidant in specified conventional food products, as described in Part 1.3 of this notice, on the basis of scientific procedures.

As detailed in Part 6, all of the pivotal data and information used to establish the safety of OS-GTE under its intended conditions of use as an antioxidant in foods are "generally available" (*i.e.,* in the public domain). All of the pivotal toxicological data used to support the safety of OS-GTE have been published by Liu *et al.* (2017), and these studies were conducted on the article of commerce. An Expert Panel reviewed proprietary manufacturing information that is not presented within the notice, specifically, information regarding the identity of the catalyst and processing aids. These materials are commonly used in food production and are recognized as such by the Expert Panel. Taking into account too that the published safety studies were conducted using OS-GTE manufactured using the same processes as those employed to produce the article of commerce, all of the data and information used to support the conclusion that OS-GTE is GRAS under its intended conditions of use are considered to be publicly available.

1.5 Availability of Information

Kemin agrees to make the data and information that are the basis for the conclusion of the GRAS status for palmitoylated green tea catechins available to the FDA, either during or after the evaluation of the GRAS notice. This data and information will be available for review and copy upon request at the address specified below during business hours:

Kemin Food Technologies
2100 Maury Street
Des Moines, IA
50317 USA

In addition, upon request, Kemin will provide the FDA with a complete copy of the data and information that are the basis for the conclusion of the GRAS status for Oil-Soluble Green Tea Extract, either in an electronic format that is accessible for the FDA's evaluation, or on paper.

1.6 Freedom of Information Act, 5 U.S.C. 552

It is Kemin's view that all data and information presented in Parts 2 through 7 of this notice do not contain any trade secret, commercial, or financial information that are privileged or confidential. Therefore, none of the data and information presented herein are exempt from the Freedom of Information Act, 5 U.S.C. Section 552.

1.7 Food Safety and Inspection Service Statement

Kemin does not intend to market Oil-Soluble Green Tea Extract as an antioxidant in meat and poultry products that are subject to regulation by the FSIS of the USDA.

Kemin Industries, Inc. 2100 Maury Street, Des Moines, IA 50317-1100 USA

November 29, 2018

CERTIFICATE OF ANALYSIS

Product 产品名 : Lipid Soluble Green Tea Extract

Lot No.批号 : 1312110858

Colour 颜色 : Off-white powder

Appearance 外观 : Fine powder

Item	*Specifications*	*Method*	*Results*
Antioxidant Capacity (as Trolox equivalent)	*Min 160*	*Internal (CUPRAC assay)*	*218.88*
Moisture (%)	*Max 5*	*GB/T 5009.3*	*1.82*
Ash (%)	*Max 1*	*GB/T 5009.4*	*0.048*
**Total Trace Elements (Copper, Iron, Manganese, Sodium and Zinc)/ppm*	*Max 250*	*USP <233>*	*7.25*

**Results were analysed by Midwest Lab*

(b) (6)

William Schroeder, PhD
Director, Research and Development

Kemin Industries, Inc. 2100 Maury Street, Des Moines, IA 50317-1100 USA

November 29, 2018

CERTIFICATE OF ANALYSIS

Product 产品名 : Lipid Soluble Green Tea Extract

Lot No.批号 : 1401101345

Colour 颜色 : Off-white powder

Appearance 外观 : Fine powder

Item	*Specifications*	*Method*	*Results*
Antioxidant Capacity (as Trolox equivalent)	*Min 160*	*Internal (CUPRAC assay)*	*193.59*
Moisture (%)	*Max 5*	*GB/T 5009.3*	*2.00*
Ash (%)	*Max 1*	*GB/T 5009.4*	*0.036*
**Total Trace Elements (Copper, Iron, Manganese, Sodium and Zinc)/ppm*	*Max 250*	*USP <233>*	*11.21*

**Results were analysed by Midwest Lab*

(b) (6)

William Schroeder, PhD
Director, Research and Development

Kemin Industries, Inc. 2100 Maury Street, Des Moines, IA 50317-1100 USA

November 29, 2018

CERTIFICATE OF ANALYSIS

Product 产品名 : Lipid Soluble Green Tea Extract

Lot No.批号 : 1711116813

Colour 颜色 : Off-white powder

Appearance 外观 : Fine powder

Item	*Specifications*	*Method*	*Results*
Antioxidant Capacity (as Trolox equivalent)	*Min 160*	*Internal (CUPRAC assay)*	*171.86*
Moisture (%)	*Max 5*	*GB/T 5009.3*	*1.16*
Ash (%)	*Max 1*	*GB/T 5009.4*	*0.060*
**Total Trace Elements (Copper, Iron, Manganese, Sodium and Zinc)/ppm*	*Max 250*	*USP <233>*	*35.38*

**Results were analysed by Midwest Lab*

(b) (6)

William Schroeder, PhD
Director, Research and Development