#796

AIBMR
Life Sciences, Inc.

June 28, 2018

Susan Carlson, PhD
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. Carlson:

In accordance with proposed regulation 21 CFR Part 170 Subpart E (Generally Recognized as Safe (GRAS) Notice), on behalf of Interquim dba Ferrer HealthTech (the notifier), we are submitting, for FDA review, the enclosed notice that Orange Extract is GRAS for use in food.

As required, one copy of the notice is provided.

Should you have any questions or concerns regarding this notice, please contact us at 253-286-2888 or info@aibmr.com.

Sincerely,

Philip A. Palmer, MS, RD (agent of the notifier)
Senior Scientific & Regulatory Consultant
AIBMR Life Sciences, Inc.

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Notice to US Food and Drug Administration of the Conclusion that the Intended Use of Orange Extract is Generally Recognized as Safe

Submitted by the Notifier:

Ferrer HealthTech
Carretera de Zeneta, 143-145
30130 Beniel (Murcia)
Spain

Prepared by the Agent of the Notifier:

AIBMR Life Sciences, Inc.
2800 E. Madison, Suite 202
Seattle WA 98112

June 28, 2018

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Figures and Tables

Part 1: Signed Statements and Certification

1.1 Submission of GRAS Notice

Ferrer HealthTech (the notifier) is submitting a new notification in accordance with 21 CFR part 170, subpart E, regarding the conclusion that Orange Extract, an aqueous extract of immature dried sweet oranges standardized to ≥ 85% hesperidin, is Generally Recognized as Safe (GRAS) for its intended use consistent with section 201 (s) of the Federal Food, Drug and Cosmetic Act.

1.2 Name and Address of the Notifier and Agent of the Notifier

Notifier

Interquim dba Ferrer HealthTech
Carretera de Zeneta, 143-145
30130 Beniel (Murcia)
Spain
Tel: +34 968 01 20 00
fht-beniel@ferrergrupo.com

Agent of the Notifier

Philip Palmer, MS, RD
Senior Scientific and Regulatory Consultant

AIBMR Life Sciences, Inc.
2800 E. Madison Street, Suite 202
Seattle, WA 98112
Tel: (253) 286-2888
info@aibmr.com

1.3 Name of the Substance

Orange Extract, standardized to ≥ 85% hesperidin (of which ≥ 85% is the 2S isomer).

1.4 Intended Conditions of Use

Orange Extract is intended to be used at an addition level of 500 mg per serving among food categories at maximum addition level concentrations specified in Part 3 of this notice. Orange Extract is not intended for use in foods where standards of identity would preclude such use, infant formula, meat, poultry, egg products, catfish, or any products that would require additional regulatory review by USDA.

1.5 Statutory Basis for GRAS Conclusion

Scientific procedures are the basis for the conclusion that the intended use of Orange Extract as an ingredient in food is GRAS.

1.6 Not Subject to Premarket Approval

We have concluded that Orange Extract is GRAS for its intended conditions of use, stated in Part 1.4 of this notice; therefore, such use of Orange Extract is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act.

1.7 Data and Information Availability Statement

The data and the information that serve as the basis for this GRAS conclusion will be available for review and copying during customary business hours at the office of Interquim (Carretera de Zeneta 143-145, 30130 Beniel (Murcia) – Spain), or will be sent to FDA upon request.

1.8 Exemption from Disclosure under the Freedom of Information Act

None of the information in Parts 2 through 7 of this GRAS notification is considered exempt from disclosure under the Freedom of Information Act (FOIA) as trade secret, personal privacy or financial information that is privileged or confidential.

1.9 Certification of Completion

We hereby certify that, to the best of our knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of Orange Extract.

(b) (6)

June 28, 2018

Francisco Borrego Ríos
Director
Interquim Beniel (Murcia)

Date

Part 2: Identity, Manufacture, Specifications, and Physical or Technical Effect

2.1 Identification

Orange Extract is composed of flavanone glycosides standardized to ≥ 85% hesperidin, with ≥ 85% of its diastereomers in the 2S configuration—the main epimer occurring in fresh oranges and orange juice. Flavanones, found in the diet almost exclusively in citrus fruits, are a class of polyphenols comprised of glycoside variations based mainly on the aglycones hesperetin (especially in oranges), naringenin (especially in grapefruit), and eriodictyol (especially in lemons).[1] Hesper*idin* (**Figure 1a)** is comprised of the aglycone hesper*etin* (**Figure 1b)** attached to the disaccharide rutinose (rhamnose + glucose). Narirutin (**Figure 2a)** is also found in Orange Extract at levels of ≤ 8%. Similarly, it is comprised of the aglycone naringenin (**Figure 2b)** attached to the disaccharide rutinose.

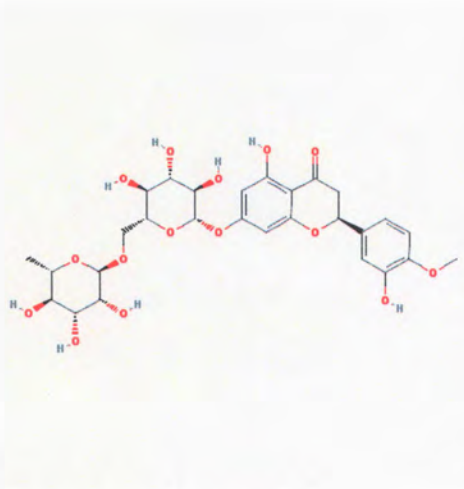


Figure 1a. Hesperidin[2]

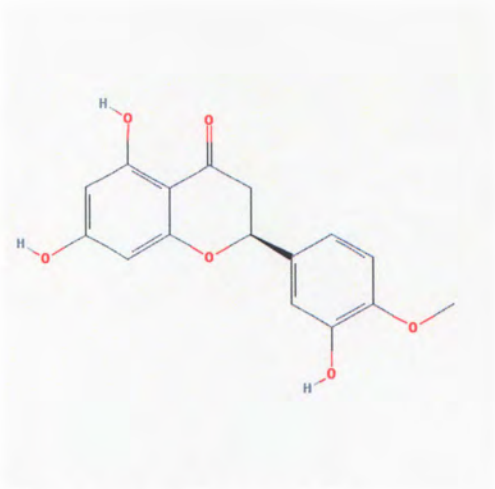


Figure 1b. Hesperetin[3]

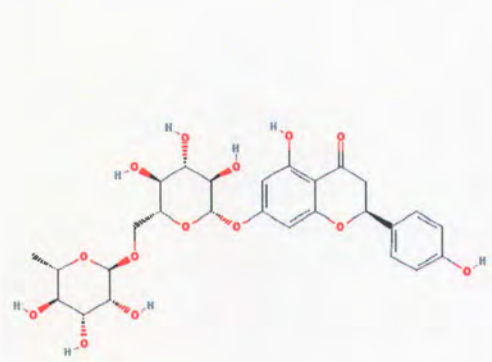


Figure 2a. Narirutin (isonaringin)[4]

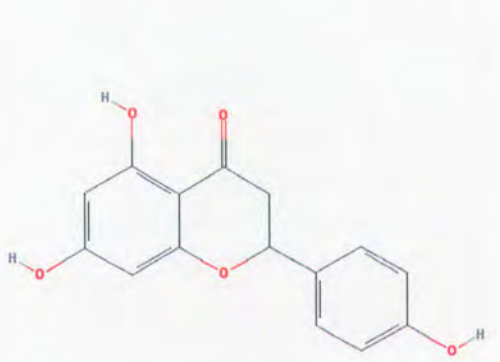


Figure 2b. Naringenin[5]

Hesperidin, CAS Registry Number 520-26-3, PubChem CID 10621, has a monoisotopic mass of 610.2 Da and a molecular formula of $C_{28}H_{34}O_{15}$. Its IUPAC name [PubChem] is (2S)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxy-2,3-dihydrochromen-4-one. As a β-7-rutinoside of hesperetin, hesperidin is also known as hesperetin 7-*O*-rutinoside. The hesperetin is attached to the glucose, and the glucose to the rhamnose.[6] Hesperidin was discovered in 1828, and is the oldest commercially available flavonoid produced from citrus fruits.[7]

Hesperidin is easily soluble in dilute alkali and in pyridine, and slightly soluble in methanol and hot glacial acetic acid. It is almost insoluble in water, acetone, benzene, and chloroform. Tan or pale yellow in color, pure crystalized hesperidin occurs as long, hair-like needles.[6] Naturally occurring hesperidin in citrus is predominantly found as the 2S configuration; hesperidin in orange juice is present in 2S:2R ratios ranging from 6.42:1 to 15.4:1.[8, 9] Orange Extract is composed of 2S and 2R hesperidin, with 2S consistently comprising 85–95% (based on historical batch data).

Sweet oranges, tangerines, and tangors are relatively high in rutinose, which conjugates to hesperidin and causes it to have a neutral taste, as opposed to the tangy or bitter taste of the glycosides neohesperidin and naringin associated with the disaccharide neohesperidose (an isomer of rutinose) that is higher in other citrus.[1, 10] Because hesperidin is practically tasteless and delays flavor deterioration

(presumably through antioxidant effects), it has been used to extend shelf life of milk-based beverages.[11]

Narirutin (isonaringin, naringenin-7-*O*-rutinoside, CAS number 14259-46-2) is also present in sweet orange (*Citrus sinensis*).[12] Not long after the compound's discovery, the term "narirutin" appears to have become favored over "isonaringin" in the scientific literature. In PubChem, the open chemistry database at the National Institutes of Health, both narirutin and isonaringin use 442431 as their PubChem Compound Identification (an accession identifier for a unique chemical structure), having the molecular formula of $C_{27}H_{32}O_{14}$ and molecular weight of 580.539 g/mol.

The remainder of Orange Extract not accounted for in the ingredient specifications (≤3%) consists of minor extractable material from the mesocarp of immature orange, such as flavonoid constituents like didymin and diosmin.

2.2 Manufacturing

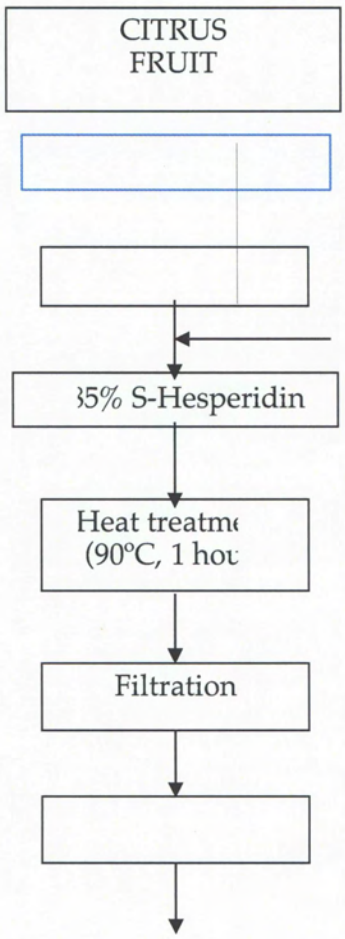
2.2.1 Good Manufacturing Practice

The Spanish Association for Standardization and Certification (AENOR) certifies that The Food Safety Management System of Interquim, S.A. (a subsidiary of Ferrer HealthTech) complies with food safety systems including ISO22000:2005, ISO/TS 22002-1, and additional FSSC 22000 requirements.

2.2.2 Manufacturing Overview

The sweet oranges used as the raw material for Orange Extract are mainly grown in the Mediterranean, Latin America, and Asia, which allows for two harvests per year. Ferrer HealthTech uses baby oranges that naturally fall to the ground after blossoming; typically, these fruits are gathered well before pesticide treatment of the trees. Once dried, care is taken to ensure that only the species *Citrus sinensis* is shipped to Ferrer HealthTech's production facility in Murcia, Spain, where the whole dried baby oranges are stored (natural ventilation) in silos. Although both exocarp and mesocarp are used in production, little of the exocarp remains; the essential oils, which are present only in very small amounts in the immature fruits, are further diminished due to evaporation when the fruits are dried.

The fully controlled process begins with growing and harvesting of immature dried fruits of sweet orange, which are submitted to alkaline aqueous extraction. Sulfuric acid is added, leading to the precipitation of S-hesperidin. The resultant product is submitted to a heat treatment, filtration and drying to yield the final Orange Extract. No material of human or animal origin is used, nor are materials irradiated at any point.


CITRUS
FRUIT
35% S-Hesperidin
Heat treatm
(90°C, 1 hou
Filtration

2.3 Specifications

The product specifications for Orange Extract, along with the specification methods, are listed in **Table 1** below.

Table 1. Orange Extract Specifications

Test Items	Specification	Method
Identification	Working standard	IR (Ph.Eur.2.2.24) and HPLC
Marker Compounds		
2S configuration diastereomers	≥ 85%	Internal method (chiral-HPLC)
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	Internal method (HPLC)
Isonaringin	≤ 8%	Internal method (HPLC)
Physical Characteristics		
Appearance	Light brown to yellowish powder with characteristic odor	Organoleptic
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	
Sulphated ash	≤ 0.2%	Current Ph.Eur. 2.4.14
Loss on drying	≤ 5%	Current Ph.Eur. 2.2.32
Heavy Metals		
Arsenic	≤ 0.2 ppm	External analysis (ICP-MS)
Cadmium	≤ 1 ppm	External analysis (ICP-MS)
Lead	≤ 0.5 ppm	External analysis (ICP-MS)
Mercury	≤ 0.1 ppm	External analysis (ICP-MS)
Microbiological Tests		
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Total Yeast & Mold	$\leq 10^2$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Salmonella	Absence in 25g	Current Ph.Eur. 2.6.12 / 2.6.13
E. coli	Absence in 1g	Current Ph.Eur. 2.6.12 / 2.6.13

Abbreviations: HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; IR, Infrared absorption spectrophotometry; Ph. Eur., European Pharmacopoeia.

2.3.1 Batch Analysis

Production conformity and consistency of Ferrer HealthTech's Orange Extract is tested in production lots. As shown in **Table 2** below, four non-consecutive batch analyses (from a 3-year period) are reasonably consistent and meet the product specifications for Orange Extract identity, physical characteristics, marker compounds, heavy metals, and microbial analyses.

Table 2. Orange Extract Batch Analysis Results

Test Items	Specification	Batch Number & Manufacturing Date			
		04D069 5.23.2014	**05D057** 5.25.2015	**016G057** 7.07.2016	**017C058** 3.28.2017
Identification	Working standard	Complies	Complies	Complies	Complies
Marker Compounds					
2S configuration diastereomers	≥ 85%	89%	85%	87%	92%
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	91.2%	91.0%	90.3%	88.7%
Isonaringin	≤ 8%	2.7%	4.4%	2.6%	5.1%
Physical Characteristics					
Appearance	Light brown to yellowish powder with characteristic odor	Complies	Complies	Complies	Complies
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	Complies	Complies	Complies	Complies
Sulphated ash	≤ 0.2%	0.14%	0.14%	0.08%	0.10%
Loss on drying	≤ 5%	3.1%	2.2%	1.9%	2.0%
Heavy Metals					
Arsenic	≤ 0.2 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm
Cadmium	≤ 1 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Lead	≤ 0.5 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Mercury	≤ 0.1 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm
Microbiological Tests					
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Complies	Complies	Complies	Complies
Total Yeast & Mold	$\leq 10^2$ cfu/g	Complies	Complies	Complies	Complies
Salmonella	Absence in 25g	Complies	Complies	Complies	Complies
E. coli	Absence in 1g	Complies	Complies	Complies	Complies

2.3.2 Residual Solvent Analysis

Water is the only solvent used in the manufacture of Orange Extract; therefore, residual solvent analysis is not necessary and is not performed.

2.3.3 Residual Pesticide Analysis

In accordance with standard operating procedures, Ferrer HealthTech certifies that production batches of Orange Extract are periodically submitted for 3rd party testing of pesticide residues and that tested batches comply with Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EECText with EEA relevance.

Immature fruits used for the production of Orange Extract are typically gathered well before pesticide treatment of the trees occurs. Nonetheless, one batch of citrus fruit is tested per year. In the case of the Orange Extract, one batch out of ten—or one batch per year if less than 10 batches are manufactured per year—is tested.

2.3.4 Shelf–Life Stability

In March 2017, long-term (60-month) and accelerated (9-month) storage condition stability testing began with samples from three batches of Orange Extract. The long-term and accelerated stability tests were conducted at 25 ± 2 °C, 60 ± 5% relative humidity and 40 ± 2 °C, 75 ± 5% relative humidity, respectively, under conditions of commercial packaging—in a small non-transparent polyethylene bag (closed with a clamp) enclosed in a larger bag and placed in metallic drum.

The measurements from the accelerated study and the 9-month time point of the long-term study were stable compared to the initial results, and fell within specifications. Additional long-term study data points will continue to be taken and analyzed. Results from sample analysis are summarized below for the accelerated (**Tables 3–5**) stability test.

Table 3. Accelerated Stability Study—Batch 016L009

ANALYSIS	INITIAL	3 MONTHS	6 MONTHS	9 MONTHS
Physical Properties				
Appearance	Complies	Complies	Complies	Complies
Loss on drying	2.4 %	2.7 %	2.3 %	2.5 %
S Isomer	92 %	91 %	92 %	92 %
Marker Compounds				
Rutinoside (Hesperidin)	92.2 %	90.6 %	90.7 %	90.5 %
Isonaringin	2.8 %	2.7 %	2.7 %	2.7 %
Microbial Purity				
Total Plate Count	Complies	Complies	Complies	Complies
Mould & Yeasts	Complies	Complies	Complies	Complies
Salmonella	Complies	Complies	Complies	Complies
E. coli	Complies	Complies	Complies	Complies

Table 4. Accelerated Stability Study—Batch 016L031

ANALYSIS	INITIAL	3 MONTHS	6 MONTHS	9 MONTHS
Physical Properties				
Appearance	Complies	Complies	Complies	Complies
Loss on drying	2.5 %	2.7 %	2.1 %	2.7 %
S Isomer	93 %	93 %	93 %	93 %
Marker Compounds				
Rutinoside (Hesperidin)	92.6 %	91.9 %	91.3 %	91.2 %
Isonaringin	2.9 %	2.8 %	2.8 %	2.9 %
Microbial Purity				
Total Plate Count	Complies	Complies	Complies	Complies

Mould & Yeasts	Complies	Complies	Complies	Complies
Salmonella	Complies	Complies	Complies	Complies
E. coli	Complies	Complies	Complies	Complies

Table 5. Accelerated Stability Study—Batch 016L049

ANALYSIS	INITIAL	3 MONTHS	6 MONTHS	9 MONTHS
Physical Properties				
Appearance	Complies	Complies	Complies	Complies
Loss on drying	2.7 %	2.8 %	2.4 %	2.7 %
S Isomer	93 %	93 %	93 %	93 %
Marker Compounds				
Rutinoside (Hesperidin)	92.5 %	92.7 %	91.5 %	91.5 %
Isonaringin	2.9 %	2.8 %	2.8 %	2.8 %
Microbial Purity				
Total Plate Count	Complies	Complies	Complies	Complies
Mould & Yeasts	Complies	Complies	Complies	Complies
Salmonella	Complies	Complies	Complies	Complies
E. coli	Complies	Complies	Complies	Complies

2.4 Physical or Technical Effect

Orange Extract is not intended to produce any physical or technical effects that are relevant to safety of the ingredient.

Part 3: Dietary Exposure

Ferrer HealthTech's Orange Extract is intended to be used as an ingredient (source of bioflavonoids) in the food categories and at the addition levels shown in **Table 6**. The extract is not intended for use in foods where standards of identity would preclude such use and is also not intended for use in infant formula, meat, poultry, non-exempt egg products, catfish, or any products that would require additional regulatory review by USDA.

Table 6. Intended Use of Orange Extract

Food Category	Average Serving Size	Maximum addition level (ppm)	Estimated amount per serving (mg)
Flavored milk and imitation milk drinks	240 mL	2083	500
Dry powdered milk mixtures (not reconstituted)	30 g	16667	500
Yogurt	225 g	2222	500
Coconut beverages	240 mL	2083	500
Cookies	30 g	16667	500
Cereal	30 g	16667	500
Cereal/granola/nutrition bars	30 g	16667	500
Fruit/fruit flavored and Vegetable Juices/drinks	240 mL	2083	500
Table fats and vegetable oils	15 mL	33333	500
Candies (chocolate and dietetic candy)	30 g	16667	500
Tea	240 mL	2083	500
Carbonated soft drinks	240 mL	2083	500
Fortified water	240 mL	2083	500
Nutrition drinks	240 mL	2083	500
Nutrition powders	30 g	16667	500
Energy drinks	240 mL	2083	500
Sports drinks	240 mL	2083	500

Exposure to hesperidin from both the background diet and from the Orange Extract intended use categories was estimated for the U.S. population using food consumption data from the What We Eat in America (WWEIA) dietary component of the National Health and Nutrition Examination Surveys (NHANES). Note that for the purpose of the calculations, it was assumed that the Orange Extract consists of 100% hesperidin, since the specification of ≥85% hesperidin allows for the ingredient to contain up to nearly 100% hesperidin. The most recent NHANES data available at the time of this writing (2013–2014) was analyzed using Creme Food Safety software 3.6 (www.cremeglobal.com). This data was obtained from 7,574 individuals that underwent two non-consecutive 24-hour dietary recall interviews (the first was collected in-person, the second by phone 3–10 days later).

WWEIA food codes that were considered most similar to the intended use categories were utilized in the assessment and were assigned the relevant intended

use concentrations. Background dietary hesperidin consumption was determined by assigning hesperidin concentrations to food codes pertaining to the juices and edible fruit of sweet orange, tangerine (mandarin), tangelo, grapefruit, lemons, and limes. The assignments were based on data from the review and assessment of analytical food composition literature compiled by Peterson et al., which provided mean hesperidin values for each fruit as mg aglycone/100 g fresh fruit or juice.[10, 14] The authors derived data on hesperidin from sweet orange from a total of 18 articles, as opposed to 5 articles on grapefruit, 4 articles on lemons, and 3 articles on limes.

Lists of the specific food codes that were utilized can be found in Appendix A. Keyword searches for *orange, tangerine, mandarin, tangelo, grapefruit, lemon*, and *lime* were used to find appropriate food codes for the Creme analysis. Food codes were not chosen if the hesperidin concentration of the food could not be estimated based on the food name; for example, the food code for "Orange-carrot juice, baby food" was not used because a concentration of hesperidin could not be estimated for the food. Aglycone values from the literature were converted to glycoside values for Creme analysis of background hesperidin consumption.

Creme software is a probabilistic modeling tool that uses high-performance computing to predict intake (including total aggregate exposure) of food groups and/or individual food ingredients. Creme Food Safety performs calculations using large-scale food consumption data sets. It bases the calculated estimates on each individual's body weight from the survey, as opposed to averaged body weights. Calculations also incorporated the NHANES assigned sample weights for each individual in the survey, which measure the number of people in the population represented by that specific subject and help to ensure that the results statistically represent the entire U.S. population. Sample weights for NHANES participants incorporate adjustments for unequal selection probabilities and certain types of non-response, as well as an adjustment to independent estimates of population sizes for specific age, sex, and race/ethnicity categories. The data is shown for "food consumers" (which includes only data from individuals who reported consuming one or more food/beverage categories intended to contain hesperidin over the two-day survey period, as opposed to the whole population). Results are given as both absolute exposure (mg/day), as well as exposure relative to body weight (mg/kg bw/day).

The relative standard error (RSE; calculated by dividing the standard error of the estimate by the estimate itself and multiplying by 100) is a statistical criterion that can be used to determine the reliability of estimates as pertains to the population (the larger the RSE the less reliable the estimate).[15] RSE values greater than 25–30% are often considered reasonable cut-offs by which to consider a value unreliable.[15, 16] For the purpose of this GRAS conclusion, an RSE value of greater than 25% was used to indicate that the estimated value was unreliable with regard to representing the population. RSE values are shown in the tables below for the 90th percentile values only, as the 90th percentile values are the most pertinent for

the exposure estimates. All of the values in the tables were considered reasonably reliable using the 25% cut-off.

Data estimated directly from the NHANES short 2-day survey do not necessarily adequately represent individual usual long-term intake due to the large amount of random error. This is because it may not correctly capture infrequent consumers. It assumes that subjects who consumed a product on a survey day consume it every day of the year, and it does not adjust for potential day-to-day variation in intake (i.e., intra-individual variation over time is not accounted for). Thus estimation of "usual" or "lifetime" exposure was also added to the model based on methodologies developed by Nusser et al., 1996, at Iowa State University.[17] This estimated lifetime data is considered the most relevant data, as GRAS exposure estimates should be based on expected regular exposure over the lifespan. The technique of estimating usual/lifetime intakes relies on the ability to transform the input daily average data (from food consumers) into normality, which is tested using the Anderson-Darling test statistic within the Creme Global software. Occasionally the Creme software determined that lifetime intake estimates required warnings; such issues are noted with asterisks in the tables and are explained below the tables—in these cases the lifetime estimates may still be used.

Estimates of the total aggregate exposures to hesperidin from the background diet in various population age groups at both the mean and 90th percentiles are shown first, in **Tables 7** and **8** below.

Table 7. Estimated Absolute Exposure to Hesperidin from the Background Diet (mg/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/day				90th % Lifetime mg/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	639 (37.6)	36.9 (2.0)	75.0 (8.3)	11.1	59.2
Teenagers	13–18	274 (30.7)	46.9 (4.2)	95.5 (11.9)	12.5	80.5*
Adults	19+	1491 (30.3)	41.5 (1.4)	85.9 (3.0)	3.5	75.2
Total Population	2+	2404 (31.4)	41.2 (1.1)	84.1 (2.8)	3.3	72.1

Creme run #258

*Creme warning -16 "Fourth moment of Usual intakes greater than 7.5", data can still be used.

Table 8. Estimated Exposure to Hesperidin from the Background Diet Relative to Body Weight (mg/kg bw/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/kg bw/day				90th % Lifetime mg/kg bw/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	639 (37.6)	1.49 (0.11)	3.26 (0.32)	9.8	2.62
Teenagers	13–18	274 (30.7)	0.72 (0.08)	1.49 (0.17)	11.4	1.29*
Adults	19+	1491 (30.3)	0.54 (0.02)	1.13 (0.05)	4.4	0.97
Total Population	2+	2404 (31.4)	0.72 (0.03)	1.51 (0.07)	4.6	1.40

Creme run #258
*Creme warning -16 "Fourth moment of Usual intakes greater than 7.5", data can still be used.

According to the background diet consumption estimates, approximately 31.4% of the total U.S. population (ages 2+) is expected to consume hesperidin from various citrus foods on a given day. The 90th percentile aggregate estimated lifetime exposure to hesperidin from the background diet for the total population was estimated at 72.1 mg/day (absolute) and 1.4 mg/kg bw/day (relative to body weight), as shown in the tables above.

Estimates derived from Creme of the total aggregate exposures to hesperidin from the background diet *plus* the Orange Extract intended uses are shown in **Tables 9** and **10** below. It should be noted that these estimates are extremely conservative, as they assume that Orange Extract/hesperidin is in 100% of the foods in the marketplace from each intended use category, at the maximum intended addition level.

Table 9. Estimated Absolute Exposure to Hesperidin from Background Diet Plus Orange Extract Intended Uses, 100% Presence Probability (mg/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/day				90th % Lifetime mg/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	1547 (95.5)	895.4 (26.0)	1678.6 (66.4)	4.0	1452.5
Teenagers	13–18	822 (95.4)	1489.6 (114.4)	2754.2 (224.42)	8.1	2614.7
Adults	19+	4358 (95.1)	1603.5 (30.6)	3265.7 (91.8)	2.8	2769.3*
Total Population	2+	6727 (95.2)	1492.4 (27.1)	3063.2 (91.4)	3.0	2608.1*

Creme run #261
*Creme warning -2048 "Number of days per person should be constant for a Foods calculation", data can still be used.

Table 10. Estimated Exposure to Hesperidin from Background Diet Plus Orange Extract Intended Uses, Relative to Body Weight, 100% Presence Probability (mg/kg bw/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/kg bw/day				90th % Lifetime mg/kg bw/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	1547 (95.5)	34.2 (1.2)	67.2 (3.1)	4.7	59.3
Teenagers	13–18	822 (95.4)	21.9 (1.5)	38.8 (2.2)	5.6	38.0
Adults	19+	4358 (95.1)	20.1 (0.4)	40.8 (1.3)	3.1	34.9*
Total Population	2+	6727 (95.2)	22.3 (0.4)	44.3 (0.8)	1.8	39.5*

Creme run #261

*Creme warning -2048 "Number of days per person should be constant for a Foods calculation", data can still be used.

According to the estimates above, approximately 95.2% of the total U.S. population (ages 2+) was identified as potential consumers of hesperidin from the background diet and/or the proposed food uses for Orange Extract. The 90th percentile aggregate estimated lifetime exposure level for the total population was 2608.1 mg/day (absolute) and 39.5 mg/kg bw/day (relative to body weight). With regard to individual population groups, the highest absolute lifetime exposure estimate was that for adults 19 years and older at the 90th percentile, at 2769.3 mg/day (**Table 9**), and the highest relative to body weight was that for children aged 2–12 years, at 59.3 mg/kg bw/day (**Table 10**).

Because of the large number of proposed intended use food categories, it is considered nearly impossible that an individual would randomly or intentionally consume a product containing the Orange Extract every single time the individual consumes a product from the intended use food categories daily over a lifetime. While food labels will list the extract as an ingredient and may even highlight the ingredient in marketing, it is assumed that many consumers will not always realize that the ingredient is present in the food. In other words, it will likely be an "invisible" ingredient to many consumers, which decreases the chance that only food products that contain the ingredient will be chosen by those consumers. Additionally, there will be cost and market share limitations of adding this specialty ingredient to foods in general, making it even less likely that an individual would consume it in all proposed food categories daily.

Thus, to calculate a more realistic hesperidin exposure estimation from the proposed food uses, an additional exposure assessment was performed that assumed an Orange Extract/hesperidin presence probability of 20% in all of the proposed food categories. The 20% presence probability factor was intended to represent an approximate 20% market share of the ingredient in each of the intended use categories, which is still considered a highly conservative assumption. The

maximum addition level for each food category was still utilized. Background hesperidin sources in the diet were left at 100% presence probability for the calculations. The resulting exposures are shown in **Tables 11** and **12** below.

Table 11. Estimated Absolute Exposure to Hesperidin from Background Diet Plus Orange Extract Intended Uses, 20% Presence Probability (mg/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/day				90th % Lifetime mg/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	1133 (69.1)	282.4 (14.5)	710.3 (65.3)	9.2	466.9
Teenagers	13–18	570 (67.5)	540.8 (107.2)	1120.3 (160.5)	14.3	915.0
Adults	19+	3009 (64.8)	467.3 (14.7)	1076.4 (31.6)	2.9	868.0
Total Population	2+	4712 (65.6)	446.0 (14.9)	1033.2 (23.8)	2.3	815.7

Creme run #262

Table 12. Estimated Exposure to Hesperidin from Background Diet Plus Orange Extract Intended Uses, Relative to Body Weight, 20% Presence Probability (mg/kg bw/day).

Population Group	Age (yrs)	Food Consumers, Daily Average mg/kg bw/day				90th % Lifetime mg/kg bw/day
		N (% total)	Mean (std err)	90th % (std err)	90th % RSE	
Children	2–12	1133 (69.1)	10.9 (0.7)	25.5 (2.4)	9.6	19.4
Teenagers	13–18	570 (67.5)	7.7 (1.4)	15.4 (1.7)	10.8	12.8
Adults	19+	3009 (64.8)	5.8 (0.2)	13.2 (0.5)	4.1	10.9
Total Population	2+	4712 (65.6)	6.8 (0.2)	15.5 (0.5)	3.2	12.8

Creme run #262

According to the estimates using a 20% presence probability, approximately 65.6% of the total U.S. population (age 2+) was identified as potential consumers of hesperidin from the background diet and/or the proposed food uses, which is still considered conservative. The 90th percentile aggregate estimated lifetime exposure for the total population was 815.7 mg/day (absolute) and 12.8 mg/kg bw/day (relative to body weight). With regard to individual population groups, the highest absolute 90th percentile lifetime exposure estimate was that for teens aged 13–18, at

915.0 mg/day. The highest lifetime exposure relative to body weight was still that for children aged 2–12, at 19.4 mg/kg bw/day.

Part 4: Self-limiting Levels of Use

Addition levels are not limited by any known factor.

Part 5: Experience Based on Common Use in Food Prior to 1958

The GRAS conclusion for Orange Extract is based on scientific procedures, and thus experience based on common use in food prior to 1958 is not considered pivotal information.

Part 6: Narrative

6.1 Authoritative Safety Opinions

6.1.1 Select Committee on GRAS Substances

The non-profit Life Sciences Research Organization (LSRO), when it was still an office within the Federation of American Societies for Experimental Biology (FASEB), assembled a group of qualified scientists designated the Select Committee of GRAS Substances (SCOGS) to prepare for FDA's Bureau of Foods a 1982 report titled, "*Evaluation of the Health Aspects of Hesperidin, Naringin, and Citrus Bioflavonoid Extracts as Food Ingredients*." The review was based partly on a monograph provided by FDA that summarized the world's scientific literature from 1920 through 1978, which was then supplemented with additional findings and expertise.[11] Animal studies summarized in the SCOGS report are discussed below, although the primary [original] research was not available for all but one (Wilson and DeEds, 1940).[18] Note that naringin is another glycoside of naringenin, bound to the disaccharide neohesperidose, versus narirutin which is bound to the disaccharide rutinose.

The review is considered pivotal for the safety of Orange Extract; it had the following conclusion: "*Hesperidin is found in all citrus fruits as well as in a number of the fruits and vegetables commonly consumed. Naringin is found in relatively large amounts in grapefruit and in other citrus fruits as well. The amount of each of these bioflavonoids normally consumed in citrus fruit and in other dietary items is several orders of magnitude greater than that added to foods as flavoring agents. Acute toxicities of purified hesperidin, hesperidin complex, and naringin are extremely low. Short-term (200 days) and long-term rat feeding studies with purified hesperidin and naringin at levels up to 2.5 g/kg bw/day have revealed no adverse effects. Both compounds have been shown to be non-mutagenic in microbial systems, and no mutagenic flavonoids have been identified as constituents of hesperidin complex. Reproduction studies conducted with a limited number of mice consuming about 2.5 g/kg bw of hesperidin complex or naringin daily indicated no adverse effect on fertility. Hesperidin complex, and purified hesperidin to a much lesser extent, have been used prophylactically and therapeutically for a variety of disorders, and is freely available without prescription. Hesperidin preparations have not proved toxic even when doses of several grams have been used daily for months or years. The Select Committee recommends that food grade specifications for hesperidin and hesperidin complex be developed. In view of the foregoing, the Select Committee concludes that: There is no evidence in the available information on hesperidin (purified or hesperidin complex) or naringin that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future*." This is known as a Type 1 conclusion by SCOGS, and it expresses the lowest level of concern about a food substance.

Commercially available preparations used in the various toxicology studies discussed in the report were described as follows:

Naringin: "derived from grapefruit peel...The naringin content of the preparation is not less than 85% with a weight loss of not more than 10% on drying. The residue on ignition is not more than 2% sulfated ash."

Hesperidin *complex*: "a crude hesperidin preparation obtained by extraction of the albedo of orange peel with calcium hydroxide solution.... On acidification with hydrochloric acid to pH about 4.5, hesperidin precipitates as a crystalline material along with other co-precipitated flavonoids. The precipitate is washed to remove non-flavonoid ballast, and then spray dried. Average hesperidin content is 72%."

Purified hesperidin: "prepared from hesperidin complex by dissolving the crystals in calcium hydroxide solution and precipitating by acidification with hydrochloric acid.... More than one cycle of dissolution and precipitation may be needed to achieve the minimum hesperidin content of 80% specified for the purified product. Most purified product is stated to have a hesperidin content of about 90%."

Among the research reported by SCOGS was evidence that hesperidin complex given by gavage to 10 young, male, Long-Evans rats did not cause death, changes in eating or drinking patterns or clinical signs over a 72-hour observation period at a dose of 16 g/kg bw. Naringin and other flavonoids also did not show acute toxicity.

In a short-term study by Deyoe et al. (1962) additionally assessed in the report, citrus bioflavonoids fed for 4 or 8 weeks to 6–8 week old chicks at dietary levels of 0.5-5.0% (approximately 0.5–5.0 g/kg body wt) led to normal growth, feed efficiency and overall mortality at levels up to 2.5% of the diet. A reduction in growth and feed utilization was noted at the 5% level. While the bioflavonoid composition was not stated, hesperidin was presumed to be the major member present.

Also reviewed in the SCOGS evaluation was a study by Wilson and DeEds (1940), in which rats were fed up to 1.0% hesperidin or naringin in a standard diet (about 1 g/kg body wt) for 200 days. The food was well tolerated (even though a bitter taste was expected from naringin). There were no significant findings with regard to food intake, growth curves, blood sugar levels or visceral weights, and no significant morphological changes were detected in the livers, hearts, spleens, adrenals, and testes of rats receiving hesperidin (they noted that tissues of animals receiving naringin were not examined histologically). Additional information about this study (not detailed in the SCOGS report) are described as follows.[18]

Three groups of six to eight male albino rats (averaging 50 grams) were given one of three dosage levels of hesperidin mixed with a stock diet: 0%, 0.0625%, and 1% by weight. Hesperidin was provided by the Los Angeles Laboratory of Fruit and Vegetable Chemistry of the Bureau of Chemistry and Soils, U.S. Department of Agriculture (it was not further described). After 150 days, weights were "within

normal limits" compared with control animals. In the final 50 days, respiratory infections throughout the population of rats complicated the growth curves. The authors state that the data provided did not permit statistical evaluation, but they believed that respiratory distress was slightly less with higher levels of hesperidin in the diet. In addition to parallel growth curves between hesperidin at all levels and controls, there were no significant differences in food intake between control rats and those receiving hesperidin. Organ weights (heart, spleen, liver, adrenals, kidneys, and testes) were all within the normal range, and macroscopic examination revealed only the lung respiratory infections. No significant morphological changes were seen in organs of animals receiving hesperidin upon histopathological examination of paraffin sections stained with hematoxylin and eosin. It was concluded that feeding of hesperidin in a standard diet at doses up to 1% (about 1 g/kg bw/day, as estimated in the 1982 SCOGS report) for 200 days "gave no evidences of cumulative injury" in male albino rats.

SCOGS also reviewed a chronic feeding study of hesperidin and other citrus flavonoid extracts, which was published in two parts based on duration (Patterson, 1960, 1961 were cited). Groups of 16 weanling female Sprague-Dawley rats were fed a control diet or diets containing 2.5% of either hesperidin (stated to be about 2–5 g/kg bw/day in the SCOGS report), lemon bioflavonoid complex (LBC), LBC concentrate (2x), LBC concentrate (6x), naringin, or orange bioflavonoid complex concentrate; half of the animals in each group were necropsied on days 70–75, and the remaining eight animals in each continued on for a 400-day duration. The mean kidney to body weight ratio for the naringin, hesperidin, and orange bioflavonoid complex concentrate groups was significantly ($p<0.05$) less than the ratio for the control group (by 9.8%, 8.6% and 6.3%, respectively), but no other significant findings were reported.

In reporting the 400-day results, no significant differences between the hesperidin and control groups were found for any of the following: body weight, hematocrit, hemoglobin level, white cell count, percent polymorphonuclear cells, lymphocytes, and mean organ to body weight ratios for the thymus, heart, lungs, spleen, kidney, liver, or uterus, except for a 13.7% increase in liver to body weight ratio in the orange bioflavonoid complex group. Histopathological examination of the heart, spleen, kidney, liver, and lower left jaw, which was not performed after necropsies on days 70–75, revealed no abnormal changes after 400 days. Consumption of the naringin diet was lower, which the authors possibly attributed to the bitter taste of the compound.

Also noted by SCOGS, "Gumbmann et al. (1978) fed neohesperidin dihydrochalcone to rats and dogs for more than 2 yr with no apparent carcinogenic or teratogenic effects."

A reproductive study, published in 1954 by Palmer and Patterson, was reviewed; mice were fed hesperidin complex or naringin. Estimated consumption ranged from 1.3–3.6 g/kg bw/day for each flavonoid. In a control period prior to adding naringin and hesperidin complex to the diet, six and eight litters were born to nine females selected for treatment, respectively. After treatment, nine and eight females gave birth to litters, respectively. No adverse effects were noted in animals continued on the diets and sacrificed at day 219 (naringin) and 158 (hesperidin complex). Few details were given, and because of contradictory tables in the original research from a subgroup of animals returned to the control diet and caged with males, SCOGS discounted data from the subgroup; also of note, SCOGS described the animals as mice initially and later in the paragraph referred to them as rats.

Lastly, SCOGS reviewed that bioflavonoid preparations have been given daily to humans for periods up to 5 years with no reported side-effects or toxic reactions. The usual dose of hesperidin has been 150–600 mg daily (about 2.5–10 mg/kg). SCOGS stated "...it is impressive that toxic effects have not been reported even when large doses were administered for many months."

6.1.2 FDA GRAS Notice 719

On December 26, 2017, an FDA no objection letter was filed for a GRAS notification submitted on behalf of PepsiCo for orange pomace and enzyme-treated orange pomace for use as an ingredient, stabilizer, thickener, and texturizing agent in various foods. The ingredients are described as a mixture of pulp and membranes that remain after peels, seeds, and juice are removed from orange fruit, with hesperidin present at a concentration of $\leq$ 3000 mg/L (actual ~626–1498 mg/L), with an estimated maximum 90th percentile exposure based on the intended uses of 8 mg/kg bw/day of hesperidin and 2 mg/kg bw/day of narirutin.

The GRAS discussed several toxicological studies on the structurally similar compound, methyl hesperidin (which they stated is 99% similar to hesperidin according to Tanimoto's structure similarity). Methyl hesperidin was found to be non-toxic and non-carcinogenic in mice when given at up to 5% in the diet for 13 to 96 weeks. A 13-week dose range-finding study of the compound also showed no toxic effects. The NOAEL determined for both the 13-week and 96-week studies was 5% in the diet, the highest dose level tested. The NOAEL in the 96-week study was stated to correspond to intake levels of 7500 mg/kg bw/day for males and 8,600 mg/kg bw/day for females. The notifiers calculated an Acceptable Daily Intake (ADI) level for hesperidin of 75 mg/kg bw/day, by using the methyl-hesperidin NOAEL of 7500 mg/kg bw/day and a 100-fold safety factor. They stated their hesperidin exposure estimate of 8 mg/kg bw/day, plus their background exposure estimate from oranges in the diet of 1 mg/kg bw/day, was well below their calculated ADI of 75 mg/kg bw/day.

6.1.3 European Food Safety Authority (EFSA)

In an evaluation of seven flavonoids conducted by the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids, hesperetin and naringin were assessed as flavoring substances used in or on foodstuffs.[19] The Panel concluded that the combined intake of hesperetin and naringin, and other flavanones do not pose a safety concern at the estimated levels of intakes arising from their use as flavoring substances. According to the Panel's default Maximised Survey-derived Daily Intake (MSDI) approach, these flavanones belonging to "structural class II" have daily per capita intakes as flavoring substances below the threshold of concern of 540 μg/person/day for a substance belonging to structural class II. Both substances were considered to be "metabolised to innocuous products".

According to the European Commission's Novel Food Catalogue, hesperidin was used only as or in food supplements before 15 May 1997, which qualifies it to not be regarded as a Novel Food, and has allowed it to be sold in dietary supplements. http://ec.europa.eu/food/safety/novel_food/catalogue/search/public/index.cfm

6.1.4 European Chemical Agency (ECHA)

ECHA manages the technical, scientific and administrative aspects of the implementation of the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. REACH was adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals.

As with GRAS Conclusions, REACH places the burden of proof on companies, who must demonstrate to ECHA how the substance can be safely used. Companies must register their substance under the "one substance, one registration" principle, which means that manufacturers and importers of the same substance must submit their registration jointly. ECHA receives and evaluates individual registrations for their compliance.

Hesperidin, EC No. 208-288-1, has full registration status, and a chemical safety assessment has been performed on the substance. No hazards have been classified according to the notifications provided by companies to ECHA in REACH registrations, or according to the majority of notifications provided by companies to ECHA in Classification, Labelling and Packaging (CLP) Regulation notifications. Hesperidin is manufactured and/or imported into the European Economic Area at 1,000–10,000 tonnes per year.

The ECHA oral route hazard assessment conclusion for hesperidin in the general population yielded a Derived No Effect Level (DNEL) of 3.75 mg/kg bw/day. This conclusion was reached based on a NOAEL of 750 mg/kg bw/day as the modified dose descriptor starting point in conjunction with an overall assessment factor of 200. The 200-day repeated dose oral study in rats implemented to reach this conclusion was not available for review by the agent of the notifier.

6.2 Pharmacokinetics of Hesperidin and Narirutin

The pharmacokinetic parameters of the flavanone glycosides hesperidin and narirutin are overall very similar, with relatively low bioavailability and metabolite T_{max} levels, and relatively large interindividual variability (possibly due to colon microbiota variations or epigenetic differences).[20-22] In a recent study comparing the pharmacokinetic profiles of hesperidin and narirutin in humans after consumption of single doses of both fresh squeezed and commercially processed juice (11.5 mL/kg bw each with a washout period of 30 days), no significant differences were found in the T_{max}, AUC or C_{max} values between the juice types. The concentrations of hesperidin and narirutin in the fresh squeezed juice were 47.2 and 5.5 mg/mL, respectively, while the concentrations in the commercially processed were 154.6 and 36.5 mg/mL, respectively. For plasma hesperitin, the AUC was 131–371 μg•h/L, the C_{max} was 16.2–57.1, the T_{max} was 4.67–5.0 h, the urine excretion was 3.76–4.13%, and total absorption was 0.8–0.9%. For plasma naringenin the AUC was 93.4–110 μg•h/L, the C_{max} was 12.5–21.5 μg/L, the T_{max} was 5.2–5.3 h, the urine excretion was 3.8–8.7%, and total absorption was 1.5–5.95%. The authors compared their results to those of other studies which showed reasonably similar results.

In a carefully controlled crossover study of five women and five men, the maximal concentration of flavanone metabolites in participants was seen 4.6–7.3 hours after consumption of five different orange juice beverages (with different flavanone concentrations) accompanied by a controlled amount of food intake.[21] The authors found that their results to be similar to those previously described suggesting the hesperetin- and naringenin-rutinosides are hydrolyzed by colonic microbiota, the aglycones of which are further absorbed and metabolized in the large intestine. In some individuals, a small proportion of unmetabolized hesperidin can be absorbed in the stomach or duodenum, as evidenced by detection in the plasma during the first 2 hours post-consumption. Urinary excretion of flavanone metabolites occurred within the first 24 hours after consumption of the beverages.

Varying plasma kinetics and urinary excretion of flavanones in humans have been gleaned from studies of orange juice ingestion.[12, 21-24] Mean peak plasma concentrations (C_{max}) for hesperitin and naringenin were 2.2 and 0.6 μM, respectively, when an orange juice providing 126 and 23 mg, respectively, was administered alone to fasted individuals.[22] Manach et al. reported that when given with a meal, an orange juice providing 220 mg of hesperitin and 45 mg of naringenin produced a mean C_{max} of 1.28 μM hesperetin and 0.2 μM naringenin.[24] The flavanone metabolites appeared in plasma 3 hours after consumption, peaked within 7 hours, and returned to baseline within 24 hours.

Again, the plasma T_{max} values of the flavanone glycosides suggest most absorption occurs in the large intestine: the disaccharide glycoside moieties of hesperetin-7-*O*-rutinoside (hesperidin) and naringenin-7-*O*-rutinoside (narirutin) are cleaved by

colonic bacteria to release the respective aglycones (herperetin and naringenin). Hesperetin is acted upon by UDP-glucuronosyltransferases in the colonocytes to produce two isomers that pass into the portal vein and are excreted in the urine along with a third hesperetin-*O*-glucuronide and six additional metabolites. Due to some metabolites accumulating in the urine in substantial amounts despite not being found in the bloodstream, much of the phase II metabolism (sulfation and further glucuronidation) is presumed to occur in the kidneys rather than the liver.[25] Sulfoglucuronide metabolites were first reported in plasma in a 2010 human bioavailability trial.[21] Similarly, Brett et al. showed that a proportion of hesperetin and naringenin from a typically consumed portion of orange fruit or processed juice are absorbed from the human gut and appear in plasma, with no significant difference in the bioavailability between the two forms but very large interindividual variation in pharmacokinetic parameters.[12] The flavanones in plasma and urine were phase-2 conjugates, the four major metabolites being 4'- and 7-glucuronides of naringenin and 3'- and 7-glucuronides of hesperetin. Gender differences have not been demonstrated in flavanone excretion after orange beverage intake.[12, 26]

Two major factors in flavanone bioavailability are the physical form when ingested (e.g., juice or capsule), and the extent of transformation during phase I, phase II, and microbiota metabolism during GI digestion and metabolism.[21] Although the percentage of intraindividual flavanone excretion remains stable, large interindividual variation in clinical research participants of at least one trial led to stratification categories of low (<5%), medium (5–10%), and high (>10%) flavanone excretion values.[26] In a study of conventional hesperidin (CHd), encapsulated hesperidin with enhanced solubility (EHd), micronized hesperidin (MHd), and micronized hesperetin (MHt), both EHd and MHd were found to be 2–3 times more bioavailable than CHd. In absolute terms, MHt reached the highest excretion values (i.e., was the most bioavailable form).[26] Stratification into categories helped assess how much of hesperidin's bioavailability depends on gut microbes, which are able to cleave hesperetin from hesperidin: a dramatic increase in urinary excretion by "low excretors" was determined to be explained by increased absorption in the small intestine (with rhamnosidases from gut microbiota not the determinant factor for absorption).

In a study of the transformation of conjugated flavonoids by colonic microbiota, the disappearance of hesperidin was associated with a stoichiometric production of hesperetin. After a 24-hour incubation with resting cells of human gut microbiota from nine healthy volunteers, a release of hesperetin in the range of 34–53% from hesperidin was found.[27] In the same study, 33 intestinal strains of *Bifidobacteria* were explored *in vitro* with the same intent; a few strains were found capable of hydrolyzing hesperidin to some extent, most notably within the species *B. pseudocatenulatum* (strain WC 0403 yielded a 46% conversion).

In a tissue distribution study of 16-week-old male Wistar rats fed 0.2% of their diet as the aglycone hesperetin for 4 weeks, hesperetin was found unequally distributed

in a wide variety of tissues and plasma. Mean (±SD) tissue levels, expressed as nmol/g tissue, were highest in the following six tissues: liver (12.97±4.66), aorta (3.11±1.40), kidneys (2.58±0.56), skin (1.85±0.64), pancreas (1.82±0.60), and spleen (1.49±0.25).[28]

Pharmacokinetic research in male Sprague-Dawley rats administered racemic hesperetin or racemic naringenin intravenously (20 mg/kg) revealed that serum and urine enantiomers were metabolized stereospecifically, however, despite the differences, all enantiomeric forms showed a rapid decline in concentration after administration, "representing a distribution phase (within the first hour) followed by steady concentrations up to 12 h and rapid elimination phase up to 72 h (last time point at which all the compounds were detected, with the exception of S(–)-hesperetin that was only detected up to 48 h)." The elimination half-lives of the parent compounds were of 3–7 h.[9]

6.3 Additional Scientific Studies

6.3.1 In vivo & in vitro studies

Mutagenicity assays (published from 1977–2011) have found hesperidin to be non-mutagenic. No hesperidin mutagenicity was observed when evaluated in *Salmonella* strains TA98 and TA100 (with and without metabolic activation) at concentrations of 200 and 2,000 nmol/plate[29] and 3,310 nmol /plate.[30] In other Ames tests, both hesperidin and hesperetin failed to induce gene mutations by base pair changes or frameshifts in the genome of the strains used under the experimental conditions applied.[31-33] More recently, a somatic mutation and recombination test (SMART) in *Drosophila melanogaster* revealed no hesperidin genotoxicity.[34]

Hesperidin showed weak antimutagenic activity against benzo[α]pyrene in a *Salmonella* microsome assay,[29] and hesperidin exhibited antigenotoxic activity against hydrogen peroxide used as a genotoxin.[34] Likely due at least in part to its antioxidant properties, hesperidin was also shown to mitigate benzo[α]pyrene induced testicular toxicity in male Swiss albino rats.[35]

A subchronic toxicity study was performed on methyl hesperidin, which is structurally similar to hesperidin.[36] Groups of 10/sex/group of B6C3F$_1$ mice were administered 0, 0.3, 0.6, 1.25, 2.5 and 5.0% of the compound in the diet for 13 weeks. One male in each of the 1.25% and 5.0% groups died during the study, however the cause of death was not attributed to the test article. In the remaining animals, while there were some sporadic findings, no significant treatment-related differences occurred in body weights, food/water consumption, hematology, clinical chemistry or organ weights. No effects of treatment were observed on gross and, histopathological examination of the major organs. The NOAEL was considered 5.0% in the diet, the highest dose tested.

A long-term carcinogenicity study was also performed on methyl hesperidin. $B6C3F_1$ mice received dietary concentrations of 0, 1.25 or 5% for 96 weeks followed by the basal diet for an additional 8 weeks.[37] Growth retardation during the experiment with final changes in organ weights occurred in females of the 1.25% group, and in both sexes of the 5.0% group. Although the organ weight differences were statistically significant, the differences compared to controls were small and no dose dependency was apparent. No biologically significant effects were evident with respect to mortality or clinical signs, and there were no changes in hematology, clinical chemistry or urinalysis parameters. On histological examination, the authors reported no significant alteration in incidence of non-neoplastic or neoplastic lesions. Methyl hesperidin was considered non-carcinogenic in the mice at up to 5% in the diet (equivalent to an average intake of 7500 mg/kg bw/day in males, and 8600 mg/kg bw/day in females).

In 5-week-old Sprague Dawley rats (weighing ~200 grams) fed a diet containing 5% or 10% hesperidin *ad libitum* for 30 days, daily food intake, body weight gain, and food efficiency were not affected by hesperidin intake.[38] In the 10% group (n=5), plasma triglycerides were significantly lower than in controls, and the amount of fecal lipid excreted was increased.

Animal research suggests hesperidin can induce antidiabetic effects. In Goto-Kaizaki (GK) weanling rats with type 2 diabetes, a 1% hesperidin diet normalized blood glucose, in part by influencing glucose-related enzymes (mRNA levels of PPAR-α and PPAR-γ were significantly ($p<0.05$) higher than among the control groups of Wistar and GK rats).[39] In C57BL/KsJ-db/db mice, a hesperidin-supplemented feed (0.2 g/kg) significantly ($p<0.05$) lowered blood glucose levels by 20% after 5 weeks. Additionally, the following markers were significantly increased, compared with the control group: hepatic glucokinase, hepatic glycogen, plasma insulin, C-peptide, and leptin.[40] In diabetic Sprague Dawley rats treated with orally administered hesperidin at 100 mg/kg/day for 4 weeks, HbA1c and blood glucose were significantly ($p<0.05$) lowered, compared with the diabetic control group.[41]

6.3.2 Human Studies

A number of human studies have been performed on hesperidin in various population groups. As summarized in **Table 13,** the monitoring of adverse events was reported in a few of the clinical trials, while in others the authors failed to specifically report safety data. A shortcoming of biological research such as these trials is that chirality is often not taken into account, so it remains unclear how the minority 2R epimer may be influencing study results, since commercially available hesperidin is a varying mixture of both stereoisomers.[42]

Table 13. Clinical Trials Reporting the Monitoring of Adverse Events

	Dose & Description	Duration	Subjects	Comments (results)
Salden, 2016 [43]	450 mg 2S hesperidin in capsules	6 weeks	n = 68 enrolled	Blood lipids, glucose, insulin not significantly altered; no safety data reported
Haidari, 2015 [44]	600 mg pure hesperidin in capsules	4 weeks	n = 75	Declaration of no serious adverse events
Rizza, 2011 [45]	500 mg 98% pure hesperidin in capsules	3 weeks	n = 28 enrolled	Declaration of no adverse effects
Kaats, 2013 [46]	200 mg hesperidin, 1152 mg naringin in capsules	60 days	n = 75	No adverse effects were reported in the study
Demonty, 2010 [47]	800 mg 80% pure hesperidin in capsules	4 weeks	n = 204	No trend toward differences among treatment groups in adverse events
Martin, 2016 [48]	500 mg* hesperidin in food (biscuits)	50 days x2	n = 12	Blood chemistry samples collected; specific safety data not reported
‡ Milenkovic, 2011 / Perche, 2014 / Morand, 2011 [49] [50] [51]	292 mg hesperidin in 500 mL drink‡	4 weeks x3	n = 24 men; same subjects in different studies	No safety data reported

*Repeatedly stated as "500 g hesperidin" in the publication; we assume 500 **mg** since 500 g seems very unlikely.
‡ Citations in this row comprise three separate publications using the same research participants.

In a 6-week randomized, double blind, placebo-controlled trial of 68 overweight or obese yet otherwise healthy men and women, 450 mg hesperidin "which contained both the S and R enantiomers in the natural 4:1 S:R ratio of hesperidin" had no significant effects on blood glucose parameters.[43] Serum glucose and plasma insulin concentrations, which were within normal blood value ranges at baseline, were not significantly altered (p=0.348 and p=0.097, respectively) by six weeks of supplementation, compared with placebo. Additionally, no significant change (p=0.225) in insulin resistance as assessed by the quantitative insulin sensitivity check index (QUICKI) was observed between groups.

Among 24 patients with metabolic syndrome, three weeks of 500 mg hesperidin (declared as 98% pure) consumption daily—in comparison to control—favorably changed blood lipid profiles (a significant decrease in total cholesterol and apoB, and an increase in HDL), endothelial function, and circulating markers of inflammation and soluble adhesion molecules (reduced concentrations of high-sensitivity C-reactive protein, serum amyloid A protein, and soluble E-selectin).[45] Of the research participants at baseline, 71% (n=17) were taking oral antidiabetic medications. Compared with the placebo, no significant differences were observed in fasting plasma glucose or fasting plasma insulin concentrations, although hesperidin treatment caused a trend (p = 0.06) toward improving insulin resistance as assessed by QUICKI.

6.4 History of Consumption

First cultivated in Southern China and Northeastern India, orange trees were introduced to Italy in the 11th century, although the Persian orange was bitter and grown primarily for medicinal purposes. In 1753, oranges were introduced in Florida via Spain.[52] On a per pound basis, oranges are the most consumed fruit in the U.S. (2013 data). Although fresh orange consumption has declined in the U.S. over the past several decades, processed orange production (mostly for juice) has grown about 2% per year since the 1960s.[53]

At approximately 15 mg per 100 g edible fruit, 2S hesperidin is the most abundant flavonoid in sweet oranges, tangelos, tangors, lemons, and limes.[54] It has been stated as being the predominant polyphenol consumed from citrus fruits and juices.[23] Based on orange juice consumption, the daily intake of flavanones has been estimated as 25–65 mg daily; this level would be higher in individuals who also consume fresh peeled oranges with at least some of the surrounding white tissues (albedo).[21] The USDA Database for Flavonoid Content of Selected Foods, Release 3.1 provides data on hesperetin (the aglycone) levels found in only a handful of foods other than citrus fruits, expressed as mg/100 g of edible portion: fresh peppermint (10.16± 0.98), red table wine (0.63±0.36), and white table wine (0.40±0.08).

At the time of the 1982 LSRO/FASEB report, orange juice was considered the primary source of hesperidin consumption, with 44 mg conservatively estimated as the per capita daily intake from that source alone. USDA data for the year 2013 shows oranges as the most commonly consumed fruit among U.S. consumers, at 3.3 pounds of fresh oranges per person and 31.3 pounds (3.6 gallons) of orange juice per person. According to the Creme analysis in Part 3 (Table 7), which is based on the most recent NHANES data available at the time of this writing (2013–2014), the 90th percentile aggregate estimated lifetime exposure to hesperidin by consumers from the background diet—with orange juice as the highest single source—for the total population (age 2+) was estimated at 72.1 mg/day (absolute).

Mid-twentieth century data published by the USDA indicated as much as 0.118 g of flavanones calculated as hesperidin (with any eriodictyol glucoside present included in the calculation as hesperidin) in 100 mL of orange juice from mature California oranges.[7] In a compilation and review of the data from analytical literature on the flavanone content of oranges, a range of 2.56–39.26 mg hesperidin aglycone per 100 g of juice or edible fruit (without rind, pith, and seeds) was calculated, with a median value of 14.19 mg and a mean value of 15.25 ± 8.21 mg.[10]

6.5 Past Sales and Reported Adverse Events

Since launching the ingredient in 2014, Ferrer HealthTech reports sales of Orange Extract in the United States and Europe as follows:

2017	2016	2015	2014
5780 kg	2775 kg	1494 kg	25 kg

Ferrer HealthTech states that no serious adverse events have been reported to date.

No FDA letters regarding concern for safety to companies that market products containing hesperidin were located. A search of MedWatch, FDA's adverse event reporting program, and FDA's Recalls, Market Withdrawals, & Safety Alerts search engine did not uncover any mention of hesperidin products.

6.6 Similar Products in the Marketplace

A general Internet search as well as searches of the National Institutes of Health (NIH) Dietary Supplements Label Database and several large distributors of dietary supplements revealed over 400 products containing hesperidin as a dietary ingredient, illustrating how widely available hesperidin products are in the United States. Despite this prevalence, we are unaware of any adverse events attributed to hesperidin. Examples of products containing hesperidin are listed in **Table 14**:

Table 14. U.S. Products Containing Hesperidin

Company	Product Name	Serving Size(s)
Swanson Premium Brand	Hesperidin	Hesperidin from *Citrus aurantium* skin **500 mg**
Allergy Research Group	WomanPrime	Hesperidin **250 mg**
Douglas Laboratories	Venasana	Hesperidin **200 mg**
HEALTH resources	Advanced Vein Support	Hesperidin **200 mg**
Natural Factors	Citrus Bioflavonoids Plus Hesperidin	Citrus bioflavanoids complex **500 mg**, Hesperidin **150 mg**

6.7 Current Regulatory Status of Hesperidin

A thorough search for the current regulatory status of hesperidin, relevant to its use in food in the United States, was conducted. Hesperidin is listed in the Everything Added to Food in the United States (EAFUS) database, indicating FDA's awareness of its use in food.

Hesperidin-containing products given prior-sanctioned status by FDA in the 20th century include:[11]

- According to SCOGS, "*Three bioflavonoid preparations were given prior-sanctioned status by FDA: naringin, hesperidin, and lemon bioflavonoid*

complex (lemon peel infusion) (Wulfsberg, 1961a). Use of these substances in amounts up to 1 g daily was authorized in special dietary foods. A subsequent decision by FDA (Wulfsberg, 1961b) accorded prior-sanctioned status to a broader range of citrus preparations; namely, 'dried concentrates of water-soluble flavonoids from washed, deoiled, ground peel and pulp of oranges, grapefruit and tangerines.' These were authorized in special dietary foods in amounts up to 600 mg daily. Hesperidin complex was stated to be GRAS by FDA when distributed over-the-counter with recommended dosages of no more than 1 g daily (Smith, 1956)."

- According to the *Encyclopedia of Food and Color Additives*, by George A. Burdock, an opinion was issued in a letter from J.H. Maryanski (FDA) to R.S. Anthony, November 26, 1985, that hesperidin is GRAS for enhancing and preserving flavor (strawberry, vanilla, and cherry-vanilla) at a level of 30 ppm in flavored milk shakes.

6.8 Basis for the GRAS Conclusion

The scientific procedures establishing the safety of Orange Extract comprise the technical element of the GRAS standard. The common knowledge element is comprised of the general availability and general acceptance, throughout the scientific community of qualified experts, of the technical element. Together, the technical element and the common knowledge element form the basis for Ferrer HealthTech's conclusion of GRAS status of Orange Extract for its intended use.

6.8.1 Technical Element

Ferrer HealthTech's aqueous Orange Extract has been the subject of a thorough safety assessment as described above. The totality of evidence supporting the safety of the extract and its individual constituents is comprised of data and information that establish their safety under the conditions of their intended use (the technical element) and data and information that is corroborative of safety. The scientific data, information, and methods forming the technical element of this conclusion are:

- The establishment of Orange Extract as a dried aqueous extract of immature dried sweet oranges comprised of $\geq$ 85% hesperidin (of which $\geq$ 85% is composed of the 2S epimer) and $\leq$ 8% isonaringin (narirutin), with the remainder of the ingredient being water and ash.
- The methods of manufacture, specifications, and batch analyses, demonstrating the safe production and high-quality control standards of the ingredient (Part 2).
- The comprehensive consumer exposure analysis for Orange Extract and background hesperidin consumption from the diet of approximately 815.7 mg/day and 12.8 mg/kg bw/day (Part 3, using a 20% presence probability),

demonstrating an adequate margin of safety/exposure compared to respective safe intake levels, which are described further below.

- The ratio of hesperidin's diastereomers in Orange Extract (85–95% 2S-hesperidin) is essentially the same as that found in orange and grapefruit juice (91–94% 2S-hesperidin).
- The pharmacokinetic properties of the flavonoid glycosides, suggesting they are hydrolyzed by gut microbiota to their respective aglycones, which have relatively low bioavailability and rapid excretion, thus are not expected to bioaccumulate.
- The opinion of SCOGS that "There is no evidence in the available information on hesperidin (purified or hesperidin complex) or naringin that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future," and their review of short-term (200 days), long-term (400 days), and reproduction toxicological studies with a NOAEL of 2–2.5 mg/kg bw/day.
- The FDA GRAS status (GRN #719) of orange pomace, with a 90th percentile hesperidin exposure estimate of 8 mg/kg bw/day and narirutin exposure estimate of 2 mg/kg bw/day, and a margin of safety for hesperidin of over 800 based on a NOAEL for methyl hesperidin of 7500 mg/kg bw/day.
- Clinical studies using levels of up to 800 mg of 80% pure hesperidin for four weeks have not resulted in adverse events.
- Hesperidin has likely been a part of the human diet since prehistoric times and is common in the U.S. food supply.
- No evidence of hesperidin toxicity in humans has been recorded despite increased consumption of sources such as orange juice and even purified hesperidin.
- There has been no evidence of serious adverse effects from Orange Extract consumption among consumers.

Among the most important data for this conclusion of GRAS status includes the Opinion of SCOGS in the LSRO/FASEB report of 1982. Although the chronic toxicity study of a purified hesperidin-containing diet versus a control diet was not conducted according to current OECD and internationally accepted standards, no "adverse effects" within a 400-day duration is nonetheless a remarkable conclusion. Unfortunately, a discrepancy appears between the concluding SCOGS Opinion and the description of the 400-day study earlier in the document. In the Opinion it is stated that, "Short-term (200 d) and long-term rat feeding studies with purified hesperidin and naringin at levels *up to 2.5 g/kg* body wt/d have revealed no adverse effects," which contrasts with the "diets containing 2.5% (about 2–5 g/kg body wt/d) [hesperidin]" stated in the "Long-term studies" section of the report. Due to this discrepancy and other factors, a 2 g/kg bw/day level is being considered here as a conservative NOAEL. The SCOGS opinion also reviewed a reproductive study in mice (1.3–3.6 g/kg bw/day), a 200-day study in male albino rats (approximately 1

g/kg bw/day) and an acute study in rats (16 g/day) without toxicological concerns, as well as several other animal studies.

Based on the intended use of Orange Extract (**Table 6**) at a maximum addition level of 500 mg per serving in various food categories, the Creme modeling data using a 20% presence probability plus estimated exposure to hesperidin from background diet reveals an estimated lifetime daily exposure level to Orange Extract at the 90th percentile for the total population as 815.7 mg/day (12.8 mg/kg bw/day). Using the NOAEL of 2000 mg/kg bw/day, based on a hesperidin extract of similar purity, and the exposure estimate of 12.8 mg/kg bw/day, a margin of safety of approximately 156 (NOAEL/exposure) can be calculated. This margin is considered reasonable based on the totality of safety evidence and history of use as summarized above, and is greater than the expected margin of safety for a food ingredient of 100 (21 CFR 170.22).

Using the methyl hesperidin NOAEL of 7500 mg/kg bw/day that was utilized to support hesperidin safety in GRN #719, an even higher margin of safety of 586 can be calculated for Orange Extract. Additionally, if the exposure estimate of hesperidin from Orange Extract plus background diet exposure is conservatively directly added to the exposure estimate of hesperidin from orange pomace from GRN #719, the total exposure would be 20.8 mg/kg bw/day, which still allows for a margin of safety of 361.

A search of the scientific literature published since the SCOGS Report revealed no new toxicology data or other information that would be considered inconsistent with the SCOGS conclusions. Overall, the totality of evidence supports a conclusion that the intended use of Orange Extract is reasonably certain to be safe when ingested by humans under the conditions of its intended use.

6.8.2 Common Knowledge Element

The scientific studies, performed in laboratory animals and humans and herein reported to provide the basis of this GRAS conclusion by scientific procedures, are published and available in the public domain. Part 7 of this GRAS notice contains the citations for the published studies. This published data fulfills the requirement for general availability of the scientific data contributing to the technical element of the GRAS standard, and provides ample evidence of consensus among qualified experts leading to reasonable certainty that consumption of Orange Extract for its intended use is not harmful. The general availability of this information satisfies the common knowledge element of this GRAS conclusion.

6.9 Data and Information that is Inconsistent with the GRAS Conclusion

The notifier is unaware of any information that would be considered inconsistent with the determination that the intended use of Orange Extract, manufactured according to GMP and meeting the specifications outlined in this dossier, is GRAS for its intended use.

6.10 Information that is Exempt from Disclosure under FOIA

There is no data or information in this GRAS notice that is considered exempt from disclosure under FOIA.

Part 7: Supporting Data and Information

7.1 Data and Information that are *not* Generally Available

All of the information described in this GRAS notice is generally available.

7.2 References that *are* Generally Available

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7.3 Appendix A. Full List of NHANES Food Codes Used for Exposure Estimates

Bolded rows indicate foods contributing to background exposure.

Food Code	Food Name
61201220	**Grapefruit juice, 100%, canned, bottled or in a carton**
61201010	**Grapefruit juice, 100%, freshly squeezed**
61201020	**Grapefruit juice, 100%, NS as to form**
61201225	**Grapefruit juice, 100%, with calcium added**
61201620	**Grapefruit juice,100%, frozen, reconstituted**
61101230	**Grapefruit, canned or frozen, in light syrup**
61101200	**Grapefruit, canned or frozen, NS as to sweetened or unsweetened; sweetened, NS as to type of sweetener**
61101220	**Grapefruit, canned or frozen, unsweetened, water pack**
61101010	**Grapefruit, raw**
61125000	**Tangelo, raw**
61104230	**Grapefruit and orange sections, cooked, canned, or frozen, in light syrup**
61104200	**Grapefruit and orange sections, cooked, canned, or frozen, NS as to added sweetener**
61104220	**Grapefruit and orange sections, cooked, canned, or frozen, unsweetened, water pack**
61104010	**Grapefruit and orange sections, raw**
61210010	**Orange juice, 100%, freshly squeezed**
61210220	**Orange juice, 100%, canned, bottled or in a carton**
61210620	**Orange juice, 100%, frozen, reconstituted**
61210000	**Orange juice, 100%, NFS**
61210250	**Orange juice, 100%, with calcium added, canned, bottled or in a carton**
61210820	**Orange juice, 100%, with calcium added, frozen, reconstituted**
67205000	**Orange juice, baby food**
61119010	**Orange, raw**
61119020	**Orange, sections, canned, juice pack**
61207200	**Lime juice, 100%, canned or bottled**
61207010	**Lime juice, 100%, freshly squeezed**
61207000	**Lime juice, 100%, NS as to form**
61116010	**Lime, raw**
61204200	**Lemon juice, 100%, canned or bottled**
61204010	**Lemon juice, 100%, freshly squeezed**
61204000	**Lemon juice, 100%, NS as to form**

61113010	**Lemon, raw**
61122350	**Orange, mandarin, canned or frozen, drained**
61122330	**Orange, mandarin, canned or frozen, in light syrup**
61122320	**Orange, mandarin, canned or frozen, juice pack**
61122300	**Orange, mandarin, canned or frozen, NS as to sweetened or unsweetened; sweetened, NS as to type of sweetener**
61213220	**Tangerine juice, 100%**
61125010	**Tangerine, raw**
61210720	**Orange juice, 100%, frozen, not reconstituted**
11350000	Almond milk, sweetened
11350010	Almond milk, sweetened, chocolate
11350020	Almond milk, unsweetened
11350030	Almond milk, unsweetened, chocolate
64101010	Apple cider
92550360	Apple juice beverage, 40-50% juice, light
64104010	Apple juice, 100%
64104030	Apple juice, 100%, with calcium added
64201010	Apricot nectar
64201500	Banana nectar
64104600	Blackberry juice, 100%
95101010	Boost Plus, nutritional drink, ready-to-drink
95101000	Boost, nutritional drink, ready-to-drink
64202010	Cantaloupe nectar
92552030	Capri Sun, fruit juice drink
92410110	Carbonated water, sweetened
92410250	Carbonated water, sweetened, with low-calorie or no-calorie sweetener
92410210	Carbonated water, unsweetened
95102000	Carnation Instant Breakfast, nutritional drink, regular, ready-to-drink
11513370	Chocolate milk, made from reduced sugar mix with fat free milk (skim)
11511300	Chocolate milk, ready to drink, fat free (skim)
11511400	Chocolate milk, ready to drink, low fat (1%)
11511200	Chocolate milk, ready to drink, reduced fat (2%)
42402010	Coconut cream (liquid expressed from grated coconut meat), canned, sweetened
11370000	Coconut milk
42401010	Coconut milk, used in cooking (liquid expressed from grated coconut meat, water added)
42404010	Coconut water, sweetened

42403010	Coconut water, unsweetened (liquid from coconuts)
92306100	Corn beverage
64100200	Cranberry juice blend, 100% juice
64100220	Cranberry juice blend, 100% juice, with calcium added
92530510	Cranberry juice drink, with high vitamin C
92550110	Cranberry juice drink, with high vitamin C, light
95311000	Energy Drink
95313200	Energy drink, sugar free
95103010	Ensure Plus, nutritional shake, ready-to-drink
95103000	Ensure, nutritional shake, ready-to-drink
92512050	Frozen daiquiri mix, from frozen concentrate, reconstituted
92512040	Frozen daiquiri mix, frozen concentrate, not reconstituted
78101100	Fruit and vegetable smoothie
78101110	Fruit and vegetable smoothie, added protein
78101120	Fruit and vegetable smoothie, bottled
92511015	Fruit flavored drink
92550620	Fruit flavored drink, diet
92541010	Fruit flavored drink, powdered, reconstituted
92552010	Fruit flavored drink, powdered, reconstituted, diet
92530410	Fruit flavored drink, with high vitamin C
92550610	Fruit flavored drink, with high vitamin C, diet
92542000	Fruit flavored drink, with high vitamin C, powdered, reconstituted
92552000	Fruit flavored drink, with high vitamin C, powdered, reconstituted, diet
92513000	Fruit flavored smoothie drink, frozen (no dairy)
92513010	Fruit flavored smoothie drink, frozen, light (no dairy)
92511250	Fruit juice beverage, 40-50% juice, citrus
64100110	Fruit juice blend, 100% juice
92510610	Fruit juice drink
92432000	Fruit juice drink, citrus, carbonated
92550040	Fruit juice drink, diet
92550035	Fruit juice drink, light
92433000	Fruit juice drink, noncitrus, carbonated
92530610	Fruit juice drink, with high vitamin C
92550030	Fruit juice drink, with high vitamin C, light
92582100	Fruit juice drink, with high vitamin C, plus added calcium
64100100	Fruit juice, NFS

64200100	Fruit nectar, NFS
92510720	Fruit punch, made with fruit juice and soda
92510730	Fruit punch, made with soda, fruit juice, and sherbet or ice cream
64134030	Fruit smoothie juice drink (no dairy)
64134200	Fruit smoothie, bottled
64134100	Fruit smoothie, light
11553100	Fruit smoothie, NFS
64134015	Fruit smoothie, with whole fruit (no dairy)
64134020	Fruit smoothie, with whole fruit (no dairy), added protein
95310200	Full Throttle Energy Drink
95320200	Gatorade G sports drink
95322200	Gatorade G2 sports drink, low calorie
94210200	Glaceau Vitamin Water
94220215	Glaceau Vitamin Water Zero
95104000	Glucerna, nutritional shake, ready-to-drink
92550200	Grape juice drink, light
64116020	Grape juice, 100%
64116060	Grape juice, 100%, with calcium added
64203020	Guava nectar
92307500	Iced Tea / Lemonade juice drink
92307520	Iced Tea / Lemonade juice drink, diet
92307510	Iced Tea / Lemonade juice drink, light
11340000	Imitation milk, non-soy, sweetened
95105000	Kellogg's Special K Protein Shake
92511000	Lemonade, frozen concentrate, not reconstituted
92510960	Lemonade, fruit flavored drink
92510955	Lemonade, fruit juice drink
92550370	Lemonade, fruit juice drink, light
11551050	Licuado / Batido (milk fruit drink)
64204010	Mango nectar
92512110	Margarita mix, nonalcoholic
75132000	Mixed vegetable juice (vegetables other than tomato)
95310400	Monster Energy Drink
95312400	Monster Energy Drink, Lo Carb
95310500	Mountain Dew AMP Energy Drink
95312500	Mountain Dew AMP Energy Drink, sugar-free

95106010	Muscle Milk, light, ready-to-drink
95106000	Muscle Milk, ready-to-drink
95310550	No Fear Energy Drink
95312550	No Fear Energy Drink, sugar-free
95310555	No Fear Motherload Energy Drink
95310560	NOS Energy Drink
95312555	NOS Energy Drink, sugar-free
95120020	Nutritional drink or meal replacement, high protein, light, ready-to-drink, NFS
95120010	Nutritional drink or meal replacement, high protein, ready-to-drink, NFS
95120050	Nutritional drink or meal replacement, liquid, soy-based
95120000	Nutritional drink or meal replacement, ready-to-drink, NFS
92550350	**Orange juice beverage, 40-50% juice, light**
64120010	Papaya juice, 100%
64210010	Papaya nectar
64121000	Passion fruit juice, 100%
64213010	Passion fruit nectar
64205010	Peach nectar
64215010	Pear nectar
93301200	Pina Colada
64124020	Pineapple juice, 100%
92550380	Pomegranate juice beverage, 40-50% juice, light
64126000	Pomegranate juice, 100%
95320500	Powerade sports drink
95322500	Powerade Zero sports drink, low calorie
94210100	Propel Water
94220110	Propel Zero Calcium Water
94220100	Propel Zero Water
95310600	Red Bull Energy Drink
95312600	Red Bull Energy Drink, sugar-free
11360000	Rice milk
95310700	Rockstar Energy Drink
95312700	Rockstar Energy Drink, sugar-free
95110020	Slim Fast Shake, meal replacement, high protein, ready-to-drink
95110000	Slim Fast Shake, meal replacement, regular, ready-to-drink
95110010	Slim Fast Shake, meal replacement, sugar free, ready-to-drink
95310750	SoBe Energize Energy Juice Drink

94210300	SoBe Life Water
94220310	SoBe Life Water Zero
92410810	Soft drink, chocolate flavored
92410820	Soft drink, chocolate flavored, diet
92410310	Soft drink, cola
92411520	Soft drink, cola, chocolate flavored
92411620	Soft drink, cola, chocolate flavored, diet
92410340	Soft drink, cola, decaffeinated
92410350	Soft drink, cola, decaffeinated, diet
92410320	Soft drink, cola, diet
92411510	Soft drink, cola, fruit or vanilla flavored
92411610	Soft drink, cola, fruit or vanilla flavored, diet
92410315	Soft drink, cola, reduced sugar
92410410	Soft drink, cream soda
92410420	Soft drink, cream soda, diet
92410550	Soft drink, fruit flavored, caffeine containing
92410560	Soft drink, fruit flavored, caffeine containing, diet
92410510	Soft drink, fruit flavored, caffeine free
92410520	Soft drink, fruit flavored, diet, caffeine free
92410610	Soft drink, ginger ale
92410620	Soft drink, ginger ale, diet
92400000	Soft drink, NFS
92400100	Soft drink, NFS, diet
92410360	Soft drink, pepper type
92410390	Soft drink, pepper type, decaffeinated
92410400	Soft drink, pepper type, decaffeinated, diet
92410370	Soft drink, pepper type, diet
92410710	Soft drink, root beer
92410720	Soft drink, root beer, diet
64221010	Soursop (Guanabana) nectar
11320000	Soy milk
11321000	Soy milk, chocolate
11320100	Soy milk, light
11321100	Soy milk, light, chocolate
11320200	Soy milk, nonfat
11321200	Soy milk, nonfat, chocolate

95323000	Sports drink, low calorie
95321000	Sports drink, NFS
64132500	Strawberry juice, 100%
11519205	Strawberry milk, fat free (skim)
11519200	Strawberry milk, low fat (1%)
11519040	Strawberry milk, NFS
11519105	Strawberry milk, reduced fat (2%)
11519050	Strawberry milk, whole
92531030	Sunny D
92582110	Sunny D, added calcium
92552020	Sunny D, reduced sugar
92510650	Tamarind drink (Refresco de tamarindo)
92306800	Tea, hot, chai, with milk
92306700	Tea, hot, chamomile
92306000	Tea, hot, herbal
92306090	Tea, hot, hibiscus
92302000	Tea, hot, leaf, black
92302500	Tea, hot, leaf, black, decaffeinated
92303010	Tea, hot, leaf, green
92303100	Tea, hot, leaf, green, decaffeinated
92304100	Tea, hot, leaf, oolong
92309000	Tea, iced, bottled, black
92309010	Tea, iced, bottled, black, decaffeinated
92309030	Tea, iced, bottled, black, decaffeinated, diet
92309050	Tea, iced, bottled, black, decaffeinated, unsweetened
92309020	Tea, iced, bottled, black, diet
92309040	Tea, iced, bottled, black, unsweetened
92309500	Tea, iced, bottled, green
92309510	Tea, iced, bottled, green, diet
92309520	Tea, iced, bottled, green, unsweetened
92308040	Tea, iced, brewed, black, decaffeinated, pre-sweetened with low calorie sweetener
92308030	Tea, iced, brewed, black, decaffeinated, pre-sweetened with sugar
92308050	Tea, iced, brewed, black, decaffeinated, unsweetened
92308010	Tea, iced, brewed, black, pre-sweetened with low calorie sweetener
92308000	Tea, iced, brewed, black, pre-sweetened with sugar
92308020	Tea, iced, brewed, black, unsweetened

92308540	Tea, iced, brewed, green, decaffeinated, pre-sweetened with low calorie sweetener
92308530	Tea, iced, brewed, green, decaffeinated, pre-sweetened with sugar
92308550	Tea, iced, brewed, green, decaffeinated, unsweetened
92308510	Tea, iced, brewed, green, pre-sweetened with low calorie sweetener
92308500	Tea, iced, brewed, green, pre-sweetened with sugar
92308520	Tea, iced, brewed, green, unsweetened
92305110	Tea, iced, instant, black, decaffeinated, pre-sweetened with low calorie sweetener
92305050	Tea, iced, instant, black, decaffeinated, pre-sweetened with sugar
92305180	Tea, iced, instant, black, decaffeinated, unsweetened
92305090	Tea, iced, instant, black, pre-sweetened with low calorie sweetner
92305040	Tea, iced, instant, black, pre-sweetened with sugar
92307400	Tea, iced, instant, black, pre-sweetened, dry
92305010	Tea, iced, instant, black, unsweetened
92307000	Tea, iced, instant, black, unsweetened, dry
92305920	Tea, iced, instant, green, pre-sweetened with low calorie sweetener
92305910	Tea, iced, instant, green, pre-sweetened with sugar
92305900	Tea, iced, instant, green, unsweetened
74303000	Tomato and vegetable juice, 100%
74303100	Tomato and vegetable juice, 100%, low sodium
74302000	Tomato juice cocktail
74301100	Tomato juice, 100%
74301150	Tomato juice, 100%, low sodium
95310800	Vault Energy Drink
95312800	Vault Zero Energy Drink
92530950	Vegetable and fruit juice drink, with high vitamin C
92550400	Vegetable and fruit juice drink, with high vitamin C, diet
92550405	Vegetable and fruit juice drink, with high vitamin C, light
78101000	Vegetable and fruit juice, 100% juice, with high vitamin C
64133100	Watermelon juice, 100%
95312900	XS Energy Drink
95312905	XS Gold Plus Energy Drink
11560000	Yoo-hoo, chocolate milk drink
11446000	Fruit and low fat yogurt parfait
11427000	Yogurt, chocolate, nonfat milk
11425000	Yogurt, chocolate, NS as to type of milk
11426000	Yogurt, chocolate, whole milk

11432000	Yogurt, fruit, low fat milk
11432500	Yogurt, fruit, low fat milk, light
11433000	Yogurt, fruit, nonfat milk
11433500	Yogurt, fruit, nonfat milk, light
11430000	Yogurt, fruit, NS as to type of milk
11431000	Yogurt, fruit, whole milk
11428000	Yogurt, Greek, chocolate, nonfat
11434010	Yogurt, Greek, fruit, low fat
11434020	Yogurt, Greek, fruit, nonfat
11434000	Yogurt, Greek, fruit, whole milk
11411410	Yogurt, Greek, plain, low fat
11411420	Yogurt, Greek, plain, nonfat milk
11411400	Yogurt, Greek, plain, whole milk
11424510	Yogurt, Greek, vanilla, low fat
11424520	Yogurt, Greek, vanilla, nonfat
11424500	Yogurt, Greek, vanilla, whole milk
11410000	Yogurt, NS as to type of milk or flavor
11411200	Yogurt, plain, low fat milk
11411300	Yogurt, plain, nonfat milk
11411010	Yogurt, plain, NS as to type of milk
11411100	Yogurt, plain, whole milk
11422000	Yogurt, vanilla, low fat milk
11422100	Yogurt, vanilla, low fat milk, light
11423000	Yogurt, vanilla, nonfat milk
11424000	Yogurt, vanilla, nonfat milk, light
11420000	Yogurt, vanilla, NS as to type of milk
11421000	Yogurt, vanilla, whole milk
57320500	100 % Natural Cereal, with oats, honey and raisins, Quaker
57321500	100 % Natural Wholegrain Cereal with raisins, lowfat, Quaker
57319000	100% Natural Cereal, plain, Quaker
57208000	All-Bran Complete Wheat Flakes, Kellogg's
53720100	Balance Original Bar
57207000	Bran Flakes, NFS (formerly 40% Bran Flakes, NFS)
53714520	Breakfast bar, cereal crust with fruit filling, lowfat
53714510	Breakfast bar, date, with yogurt coating
53714500	Breakfast bar, NFS

95201000	Carnation Instant Breakfast, nutritional drink mix, regular, powder
95201010	Carnation Instant Breakfast, nutritional drink mix, sugar free, powder
57000000	Cereal, NFS
57100100	Cereal, ready-to-eat, NFS
11830160	Chocolate beverage powder, dry mix, not reconstituted
11830165	Chocolate beverage powder, reduced sugar, dry mix, not reconstituted
91705300	Chocolate, sweet or dark
53720200	Clif Bar
53720210	Clif Kids Organic Zbar
11830150	Cocoa powder, not reconstituted (no dry milk)
53211000	Cookie bar, with chocolate, nuts, and graham crackers
53205260	Cookie, bar, with chocolate
53241600	Cookie, butter or sugar, with fruit and/or nuts
53220030	Cookie, fig bar
53220040	Cookie, fig bar, fat free
53220000	Cookie, fruit-filled bar
53220010	Cookie, fruit-filled bar, fat free
53223100	Cookie, granola
53231400	Cookie, multigrain, high fiber
53233000	Cookie, oatmeal
53233040	Cookie, oatmeal, reduced fat, NS as to raisins
53233010	Cookie, oatmeal, with raisins
53236100	Cookie, pumpkin
53237000	Cookie, raisin
57135000	Corn flakes, Kellogg's
57134000	Corn flakes, NFS
57143500	Cranberry Almond Crunch, Post
91770030	Dietetic or low calorie candy, chocolate covered
91770000	Dietetic or low calorie candy, NFS
91770010	Dietetic or low calorie gumdrops
91770020	Dietetic or low calorie hard candy
95201300	EAS Soy Protein Powder
95201200	EAS Whey Protein Powder
57206800	Fiber 7 Flakes, Health Valley
57206700	Fiber One
53710400	Fiber One Chewy Bar

57206715	Fiber One Raisin Bran Clusters
57221000	Fruit & Fibre (fiber) with dates, raisins, and walnuts
57219000	Fruit & Fibre (fiber), NFS
53714220	Granola bar with nuts, chocolate-coated
53714200	Granola bar, chocolate-coated, NFS
53714250	Granola bar, coated with non-chocolate coating
53714300	Granola bar, high fiber, coated with non-chocolate yogurt coating
53712200	Granola bar, lowfat, NFS
53712100	Granola bar, NFS
53712210	Granola bar, nonfat
53714230	Granola bar, oats, nuts, coated with non-chocolate coating
53713100	Granola bar, peanuts , oats, sugar, wheat germ
53713000	Granola bar, reduced sugar, NFS
53714210	Granola bar, with coconut, chocolate-coated
53714400	Granola bar, with rice cereal
57229500	Granola with Raisins, lowfat, Kellogg's
57229000	Granola, lowfat, Kellogg's
57227000	Granola, NFS
57231250	Great Grains Double Pecan Whole Grain Cereal, Post
57231200	Great Grains, Raisin, Date, and Pecan Whole Grain Cereal, Post
95201500	Herbalife, nutritional shake mix, high protein, powder
11830115	Hot chocolate / Cocoa, dry mix, no sugar added, not reconstituted
11830100	Hot chocolate / Cocoa, dry mix, not reconstituted
95201600	Isopure protein powder
57301505	Kashi Autumn Wheat
57000050	Kashi cereal, NS as to ready to eat or cooked
53710800	Kashi GOLEAN Chewy Bars
53710804	Kashi GOLEAN Crunchy Bars
53710802	Kashi TLC Chewy Granola Bar
53710806	Kashi TLC Crunchy Granola Bar
57301500	Kashi, Puffed
53710500	Kellogg's Nutri-Grain Cereal Bar
53710504	Kellogg's Nutri-Grain Fruit and Nut Bar
53710502	Kellogg's Nutri-Grain Yogurt Bar
53710700	Kellogg's Special K bar
95201700	Kellogg's Special K20 Protein Water Mix

53241510	Marie biscuit
53710600	Milk 'n Cereal bar
11813000	Milk, dry, not reconstituted, fat free (skim)
11812000	Milk, dry, not reconstituted, low fat (1%)
11810000	Milk, dry, not reconstituted, NS as to fat content
11811000	Milk, dry, not reconstituted, whole
11830260	Milk, malted, dry mix, not reconstituted
57308190	Muesli, dried fruit and nuts (formerly Muesli with raisins, dates, and almonds)
57308150	Mueslix cereal, NFS
95202010	Muscle Milk, light, powder
95202000	Muscle Milk, regular, powder
57209000	Natural Bran Flakes, Post (formerly called 40% Bran Flakes, Post)
53710902	Nature Valley Chewy Granola Bar with Yogurt Coating
53710900	Nature Valley Chewy Trail Mix Granola Bar
53710906	Nature Valley Crunchy Granola Bar
57309100	Nature Valley Granola, with fruit and nuts
53710904	Nature Valley Sweet and Salty Granola Bar
53729000	Nutrition bar or meal replacement bar, NFS
95220010	Nutritional drink mix or meal replacement, high protein, powder, NFS
95220000	Nutritional drink mix or meal replacement, powder, NFS
57316300	Oat Bran Flakes, Health Valley
57000100	Oat cereal, NFS
57316450	Oatmeal Crisp with Almonds
57321900	Organic Flax Plus, Nature's Path
53720300	PowerBar
95230020	Protein powder, light, NFS
95230030	Protein powder, NFS
95230010	Protein powder, soy based, NFS
95230000	Protein powder, whey based, NFS
53711004	Quaker Chewy 25% Less Sugar Granola Bar
53711002	Quaker Chewy 90 Calorie Granola Bar
53711006	Quaker Chewy Dipps Granola Bar
53711000	Quaker Chewy Granola Bar
53711100	Quaker Granola Bites
57327450	Quaker Oat Bran Cereal
57327500	Quaker Oatmeal Squares (formerly Quaker Oat Squares)

57349020	Reduced Sugar Frosted Flakes Cereal, Kellogg's
53720400	Slim Fast Original Meal Bar
95210020	Slim Fast Shake Mix, high protein, powder
95210000	Slim Fast Shake Mix, powder
95210010	Slim Fast Shake Mix, sugar free, powder
53712000	Snack bar, oatmeal
53720500	Snickers Marathon Protein bar
53720610	South Beach Living High Protein Bar
53720600	South Beach Living Meal Bar
57344000	Special K
57344007	Special K Low Fat Granola
57344010	Special K Red Berries
11830400	Strawberry beverage powder, dry mix, not reconstituted
53720700	Tiger's Milk bar
57410000	Weetabix Whole Wheat Cereal
11825000	Whey, sweet, dry
53720800	Zone Perfect Classic Crunch nutrition bar
81104110	Margarine-like spread, fat free, liquid, salted
81104100	Margarine-like spread, fat free, tub, salted
81103090	Margarine-like spread, liquid, salted
81103041	Margarine-like spread, made with yogurt, stick, salted
81104050	Margarine-like spread, reduced calorie, about 20% fat, tub, salted
81104011	Margarine-like spread, reduced calorie, about 40% fat, made with yogurt, tub, salted
81104020	Margarine-like spread, reduced calorie, about 40% fat, stick, salted
81104010	Margarine-like spread, reduced calorie, about 40% fat, tub, salted
81103040	Margarine-like spread, stick, salted
81103100	Margarine-like spread, stick, unsalted
81103080	Margarine-like spread, tub, salted
81103140	Margarine-like spread, tub, sweetened
81103120	Margarine-like spread, tub, unsalted
81103130	Margarine-like spread, whipped, tub, salted
82104000	Olive oil
81104550	Vegetable oil-butter spread, reduced calorie, stick, salted
81104560	Vegetable oil-butter spread, reduced calorie, tub, salted
81104500	Vegetable oil-butter spread, stick, salted
81104510	Vegetable oil-butter spread, tub, salted

Bonnette, Richard

From: Jared Brodin <Jared@aibmr.com>
Sent: Wednesday, July 11, 2018 3:08 PM
To: Bonnette, Richard
Subject: Re: your submission to the FDA GRAS notification program for orange extract
Attachments: Ferrer FDA GRAS 2018.pdf

Mr. Bonnette,

Apologies for this! I've attached the pages around and including 11 – please let me know if you need anything further.

Jared

Jared Douglas Brodin
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(253) 286-2888
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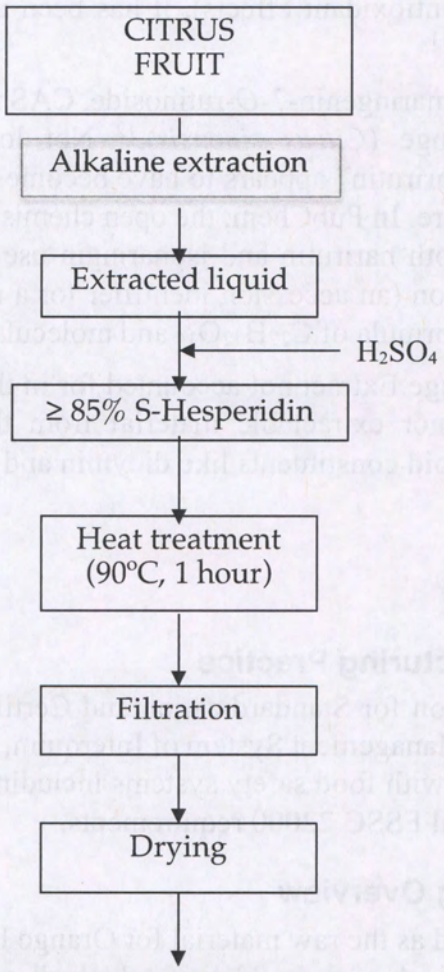
From: "Bonnette, Richard" <Richard.Bonnette@fda.hhs.gov>
Date: Tuesday, July 10, 2018 at 10:26 AM
To: "info@aibmr.com" <info@aibmr.com>
Subject: your submission to the FDA GRAS notification program for orange extract

Mr. Palmer,
We received your submission on behalf of Ferrer HeathTech regarding GRAS status for uses of orange extract in food on July 2, 2018. During the preliminary review, it was noted that the manufacturing flow chart on page 11 seems to be missing information. Several boxes in the flow chart are blank and there is other information obviously missing. Perhaps there was an error when this page was printed? Can you provide a revised version? Feel free to email a pdf of page 11 to me and I will add it to the current submission. Let me know if you have any questions.
Regards,
Richard

Richard E. Bonnette, M.S.
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 240-402-1235
richard.bonnette@fda.hhs.gov


CITRUS
FRUIT
Alkaline extraction
Extracted liquid
H_2SO_4
≥ 85% S-Hesperidin
Heat treatment
(90°C, 1 hour)
Filtration
Drying
Orange Extract

(presumably through antioxidant effects), it has been used to extend shelf life of milk-based beverages.[11]

Narirutin (isonaringin, naringenin-7-*O*-rutinoside, CAS number 14259-46-2) is also present in sweet orange (*Citrus sinensis*).[12] Not long after the compound's discovery, the term "narirutin" appears to have become favored over "isonaringin" in the scientific literature. In PubChem, the open chemistry database at the National Institutes of Health, both narirutin and isonaringin use 442431 as their PubChem Compound Identification (an accession identifier for a unique chemical structure), having the molecular formula of $C_{27}H_{32}O_{14}$ and molecular weight of 580.539 g/mol.

The remainder of Orange Extract not accounted for in the ingredient specifications (≤3%) consists of minor extractable material from the mesocarp of immature orange, such as flavonoid constituents like didymin and diosmin.

2.2 Manufacturing

2.2.1 Good Manufacturing Practice

The Spanish Association for Standardization and Certification (AENOR) certifies that The Food Safety Management System of Interquim, S.A. (a subsidiary of Ferrer HealthTech) complies with food safety systems including ISO22000:2005, ISO/TS 22002-1, and additional FSSC 22000 requirements.

2.2.2 Manufacturing Overview

The sweet oranges used as the raw material for Orange Extract are mainly grown in the Mediterranean, Latin America, and Asia, which allows for two harvests per year. Ferrer HealthTech uses baby oranges that naturally fall to the ground after blossoming; typically, these fruits are gathered well before pesticide treatment of the trees. Once dried, care is taken to ensure that only the species *Citrus sinensis* is shipped to Ferrer HealthTech's production facility in Murcia, Spain, where the whole dried baby oranges are stored (natural ventilation) in silos. Although both exocarp and mesocarp are used in production, little of the exocarp remains; the essential oils, which are present only in very small amounts in the immature fruits, are further diminished due to evaporation when the fruits are dried.

The fully controlled process begins with growing and harvesting of immature dried fruits of sweet orange, which are submitted to alkaline aqueous extraction. Sulfuric acid is added, leading to the precipitation of S-hesperidin. The resultant product is submitted to a heat treatment, filtration and drying to yield the final Orange Extract. No material of human or animal origin is used, nor are materials irradiated at any point.

Table 2. Orange Extract Batch Analysis Results

Test Items	Specification	Batch Number & Manufacturing Date			
		04D069 5.23.2014	**05D057** 5.25.2015	**016G057** 7.07.2016	**017C058** 3.28.2017
Identification	Working standard	Complies	Complies	Complies	Complies
Marker Compounds					
2S configuration diastereomers	≥ 85%	89%	85%	87%	92%
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	91.2%	91.0%	90.3%	88.7%
Isonaringin	≤ 8%	2.7%	4.4%	2.6%	5.1%
Physical Characteristics					
Appearance	Light brown to yellowish powder with characteristic odor	Complies	Complies	Complies	Complies
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	Complies	Complies	Complies	Complies
Sulphated ash	≤ 0.2%	0.14%	0.14%	0.08%	0.10%
Loss on drying	≤ 5%	3.1%	2.2%	1.9%	2.0%
Heavy Metals					
Arsenic	≤ 0.2 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm
Cadmium	≤ 1 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Lead	≤ 0.5 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Mercury	≤ 0.1 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm
Microbiological Tests					
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Complies	Complies	Complies	Complies
Total Yeast & Mold	$\leq 10^2$ cfu/g	Complies	Complies	Complies	Complies
Salmonella	Absence in 25g	Complies	Complies	Complies	Complies
E. coli	Absence in 1g	Complies	Complies	Complies	Complies

2.3.2 Residual Solvent Analysis

Water is the only solvent used in the manufacture of Orange Extract; therefore, residual solvent analysis is not necessary and is not performed.

2.3.3 Residual Pesticide Analysis

In accordance with standard operating procedures, Ferrer HealthTech certifies that production batches of Orange Extract are periodically submitted for 3rd party testing of pesticide residues and that tested batches comply with Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EECText with EEA relevance.

2.3 Specifications

The product specifications for Orange Extract, along with the specification methods, are listed in **Table 1** below.

Table 1. Orange Extract Specifications

Test Items	Specification	Method
Identification	Working standard	IR (Ph.Eur.2.2.24) and HPLC
Marker Compounds		
2S configuration diastereomers	≥ 85%	Internal method (chiral-HPLC)
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	Internal method (HPLC)
Isonaringin	≤ 8%	Internal method (HPLC)
Physical Characteristics		
Appearance	Light brown to yellowish powder with characteristic odor	Organoleptic
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	
Sulphated ash	≤ 0.2%	Current Ph.Eur. 2.4.14
Loss on drying	≤ 5%	Current Ph.Eur. 2.2.32
Heavy Metals		
Arsenic	≤ 0.2 ppm	External analysis (ICP-MS)
Cadmium	≤ 1 ppm	External analysis (ICP-MS)
Lead	≤ 0.5 ppm	External analysis (ICP-MS)
Mercury	≤ 0.1 ppm	External analysis (ICP-MS)
Microbiological Tests		
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Total Yeast & Mold	$\leq 10^2$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Salmonella	Absence in 25g	Current Ph.Eur. 2.6.12 / 2.6.13
E. coli	Absence in 1g	Current Ph.Eur. 2.6.12 / 2.6.13

Abbreviations: HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; IR, Infrared absorption spectrophotometry; Ph. Eur., European Pharmacopoeia.

2.3.1 Batch Analysis

Production conformity and consistency of Ferrer HealthTech's Orange Extract is tested in production lots. As shown in **Table 2** below, four non-consecutive batch analyses (from a 3-year period) are reasonably consistent and meet the product specifications for Orange Extract identity, physical characteristics, marker compounds, heavy metals, and microbial analyses.

Bonnette, Richard

From: Jared Brodin <Jared@aibmr.com>
Sent: Wednesday, July 11, 2018 3:08 PM
To: Bonnette, Richard
Subject: Re: your submission to the FDA GRAS notification program for orange extract
Attachments: Ferrer FDA GRAS 2018.pdf

Mr. Bonnette,

Apologies for this! I've attached the pages around and including 11 – please let me know if you need anything further.

Jared

Jared Douglas Brodin
Director of Information Services
AIBMR Life Sciences, Inc.
2800 E. Madison St., Suite 202
Seattle, WA 98112
(253) 286-2888
www.aibmr.com
Follow us on Twitter! @AIBMRinc

From: "Bonnette, Richard" <Richard.Bonnette@fda.hhs.gov>
Date: Tuesday, July 10, 2018 at 10:26 AM
To: "info@aibmr.com" <info@aibmr.com>
Subject: your submission to the FDA GRAS notification program for orange extract

Mr. Palmer,
We received your submission on behalf of Ferrer HeathTech regarding GRAS status for uses of orange extract in food on July 2, 2018. During the preliminary review, it was noted that the manufacturing flow chart on page 11 seems to be missing information. Several boxes in the flow chart are blank and there is other information obviously missing. Perhaps there was an error when this page was printed? Can you provide a revised version? Feel free to email a pdf of page 11 to me and I will add it to the current submission. Let me know if you have any questions.
Regards,
Richard

Richard E. Bonnette, M.S.
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
Tel: 240-402-1235
richard.bonnette@fda.hhs.gov

(presumably through antioxidant effects), it has been used to extend shelf life of milk-based beverages.[11]

Narirutin (isonaringin, naringenin-7-*O*-rutinoside, CAS number 14259-46-2) is also present in sweet orange (*Citrus sinensis*).[12] Not long after the compound's discovery, the term "narirutin" appears to have become favored over "isonaringin" in the scientific literature. In PubChem, the open chemistry database at the National Institutes of Health, both narirutin and isonaringin use 442431 as their PubChem Compound Identification (an accession identifier for a unique chemical structure), having the molecular formula of $C_{27}H_{32}O_{14}$ and molecular weight of 580.539 g/mol.

The remainder of Orange Extract not accounted for in the ingredient specifications (≤3%) consists of minor extractable material from the mesocarp of immature orange, such as flavonoid constituents like didymin and diosmin.

2.2 Manufacturing

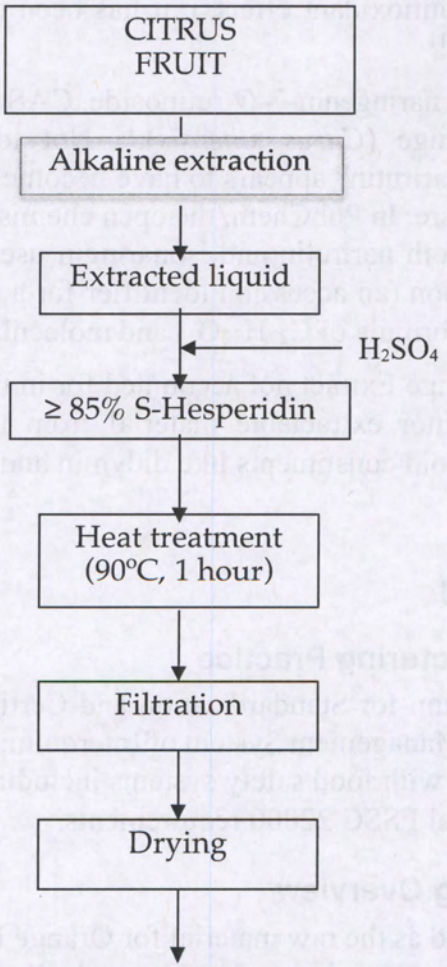
2.2.1 Good Manufacturing Practice

The Spanish Association for Standardization and Certification (AENOR) certifies that The Food Safety Management System of Interquim, S.A. (a subsidiary of Ferrer HealthTech) complies with food safety systems including ISO22000:2005, ISO/TS 22002-1, and additional FSSC 22000 requirements.

2.2.2 Manufacturing Overview

The sweet oranges used as the raw material for Orange Extract are mainly grown in the Mediterranean, Latin America, and Asia, which allows for two harvests per year. Ferrer HealthTech uses baby oranges that naturally fall to the ground after blossoming; typically, these fruits are gathered well before pesticide treatment of the trees. Once dried, care is taken to ensure that only the species *Citrus sinensis* is shipped to Ferrer HealthTech's production facility in Murcia, Spain, where the whole dried baby oranges are stored (natural ventilation) in silos. Although both exocarp and mesocarp are used in production, little of the exocarp remains; the essential oils, which are present only in very small amounts in the immature fruits, are further diminished due to evaporation when the fruits are dried.

The fully controlled process begins with growing and harvesting of immature dried fruits of sweet orange, which are submitted to alkaline aqueous extraction. Sulfuric acid is added, leading to the precipitation of S-hesperidin. The resultant product is submitted to a heat treatment, filtration and drying to yield the final Orange Extract. No material of human or animal origin is used, nor are materials irradiated at any point.


CITRUS FRUIT
Alkaline extraction
Extracted liquid
H_2SO_4
≥ 85% S-Hesperidin
Heat treatment (90°C, 1 hour)
Filtration
Drying
Orange Extract

2.3 Specifications

The product specifications for Orange Extract, along with the specification methods, are listed in **Table 1** below.

Table 1. Orange Extract Specifications

Test Items	Specification	Method
Identification	Working standard	IR (Ph.Eur.2.2.24) and HPLC
Marker Compounds		
2S configuration diastereomers	≥ 85%	Internal method (chiral-HPLC)
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	Internal method (HPLC)
Isonaringin	≤ 8%	Internal method (HPLC)
Physical Characteristics		
Appearance	Light brown to yellowish powder with characteristic odor	Organoleptic
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	
Sulphated ash	≤ 0.2%	Current Ph.Eur. 2.4.14
Loss on drying	≤ 5%	Current Ph.Eur. 2.2.32
Heavy Metals		
Arsenic	≤ 0.2 ppm	External analysis (ICP-MS)
Cadmium	≤ 1 ppm	External analysis (ICP-MS)
Lead	≤ 0.5 ppm	External analysis (ICP-MS)
Mercury	≤ 0.1 ppm	External analysis (ICP-MS)
Microbiological Tests		
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Total Yeast & Mold	$\leq 10^2$ cfu/g	Current Ph.Eur. 2.6.12 / 2.6.13
Salmonella	Absence in 25g	Current Ph.Eur. 2.6.12 / 2.6.13
E. coli	Absence in 1g	Current Ph.Eur. 2.6.12 / 2.6.13

Abbreviations: HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; IR, Infrared absorption spectrophotometry; Ph. Eur., European Pharmacopoeia.

2.3.1 Batch Analysis

Production conformity and consistency of Ferrer HealthTech's Orange Extract is tested in production lots. As shown in **Table 2** below, four non-consecutive batch analyses (from a 3-year period) are reasonably consistent and meet the product specifications for Orange Extract identity, physical characteristics, marker compounds, heavy metals, and microbial analyses.

Table 2. Orange Extract Batch Analysis Results

Test Items	Specification	Batch Number & Manufacturing Date			
		04D069 5.23.2014	**05D057** 5.25.2015	**016G057** 7.07.2016	**017C058** 3.28.2017
Identification	Working standard	Complies	Complies	Complies	Complies
Marker Compounds					
2S configuration diastereomers	≥ 85%	89%	85%	87%	92%
Rutinoside (Hesperidin) (on anhydrous basis)	≥ 85%	91.2%	91.0%	90.3%	88.7%
Isonaringin	≤ 8%	2.7%	4.4%	2.6%	5.1%
Physical Characteristics					
Appearance	Light brown to yellowish powder with characteristic odor	Complies	Complies	Complies	Complies
Solubility	Almost insoluble in water. Slightly soluble in alcohols and freely soluble in diluted alkali.	Complies	Complies	Complies	Complies
Sulphated ash	≤ 0.2%	0.14%	0.14%	0.08%	0.10%
Loss on drying	≤ 5%	3.1%	2.2%	1.9%	2.0%
Heavy Metals					
Arsenic	≤ 0.2 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm	< 0.10 ppm
Cadmium	≤ 1 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Lead	≤ 0.5 ppm	< 0.10 ppm	< 0.25 ppm	< 0.10 ppm	< 0.10 ppm
Mercury	≤ 0.1 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm	< 0.050 ppm
Microbiological Tests					
Total Aerobic Microbial	$\leq 10^3$ cfu/g	Complies	Complies	Complies	Complies
Total Yeast & Mold	$\leq 10^2$ cfu/g	Complies	Complies	Complies	Complies
Salmonella	Absence in 25g	Complies	Complies	Complies	Complies
E. coli	Absence in 1g	Complies	Complies	Complies	Complies

2.3.2 Residual Solvent Analysis

Water is the only solvent used in the manufacture of Orange Extract; therefore, residual solvent analysis is not necessary and is not performed.

2.3.3 Residual Pesticide Analysis

In accordance with standard operating procedures, Ferrer HealthTech certifies that production batches of Orange Extract are periodically submitted for 3rd party testing of pesticide residues and that tested batches comply with Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EECText with EEA relevance.

Kolanos, Renata

From: John Endres <john@aibmr.com>
Sent: Friday, September 14, 2018 10:24 PM
To: Kolanos, Renata
Cc: Amy Clewell
Subject: AIBMR: FDA Questions response regarding GRN 000796
Attachments: GRN 000796—answers to FDA questions 14Sep2018.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Dr. Kolanos,

As requested, please find our responses attached as a pdf document. If you would like this in some other form of communication, please let me know.

Feel free to contact me at any time at this email address or on my mobile phone: (b) (6) .

Thanks very much in advance!

Best Regards,
John

Celebrating our 40th Anniversary!

John R. Endres, ND
Chief Scientific Officer
AIBMR Life Sciences, Inc.
Ph. (253) 286-2888
www.aibmr.com
www.toxicoop.com

Visit AIBMR at 4129
SupplySide WEST
November 8–9, 2018

1. On page 5 of the notice, the notifier states that orange extract is ≥85% hesperidin, of which ≥85% is the 2S-isomer. The specifications in Table 1 of the notice include limits of ≥85% for both "2S configuration diastereomers" and "rutinoside (hesperidin)." Please confirm whether the specification for 2S diastereomers is based on total weight of orange extract or of total hesperidin.
Response: The total orange extract is ≥ 85% hesperidin, and ≥ 85% of that hesperidin is as 2S diastereomers

2. Please provide the full primary reference for the following studies and abbreviated references not listed in your References section (Please note that the SCOGS report and GRN 000719 are only secondary references for these studies.):
a) The acute toxicity study on page 26.
b) The short-term study by Deyoe et al. (1962) on page 26.
c) The chronic feeding study by Patterson, 1960, 1961, and 1962 on page 27.
d) The reproductive study by Palmer and Patterson, 1954 on page 28.

Responses:
a) Primorganics, Inc. 1955. Culver City, CA. Acute oral toxicity of hesperidin complex and lemon bioflavonoid complex in rats. Copies of reports submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD, by Sunkist Growers, Inc., Ontario, CA.
and
Primorganics, Inc. 1956. Culver City, CA. Acute oral toxicity of lemon bioflavonoid complex and lemon-orange flavonate glycoside in rats. Copies of reports submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD, by Sunkist Growers, Inc., Ontario, CA.

b) Deyoe, C.W.; Deacon, L.E.; Couch, J.R. 1962. Citrus bioflavonoids in broiler diets. Poult. Sci. 41:1088-1090.

c) Patterson, J.A. 1960. Sunkist Growers, Inc., Ontario, CA. Flavonoid feeding studies. A 75 day interim examination of a 400 day study. Copy of report submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD.
and
Patterson, J.A. 1961. Sunkist Growers, Inc., Ontario, CA. Flavonoid feeding series no. 1. Final report on 400 day chronic toxicity study on rats. Report 2. Copy of report submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD. 13p.
and
Patterson, J.A. 1962. Sunkist Growers, Inc., Ontario, CA. Flavonoid feeding study, series no. 2. Final report on the 400 day chronic oral toxicity study. Copy of report submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD. 14p.

d) Palmer, G.H.; Patterson, J.A. 1954. Sunkist Growers, Inc., Ontario, CA. A study of the effect of bioflavonoids on mouse fertility. Copy of report submitted to Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD.

3. On page 27, the notifier states "SCOGS also reviewed a chronic feeding study of hesperidin and other citrus flavonoid extracts, which were published in two parts based on duration (Patterson, 1960, 1961 were cited)."

Responses:
a) FDA notes that the results of this study were reported in three parts: Patterson 1960, 1961, and 1962. The notifier even provides information from the 1962 report. Please confirm that you agree.
b) FDA notes that these reports are unpublished. Please confirm.

a) We agree. Originally, our focus on only hesperidin led us to choose omitting the 1962 paper in discussion; subsequently, we decided a broader perspective was beneficial, but neglected to fully update the narrative to reflect that.
b) Yes, it appears that copies of these reports were submitted to LSRO, but we were not successful in finding published versions of these reports/studies. We contacted Michael Falk (President) at LSRO and received this reply: "*None of those files are around anymore. The only files left are the final reports. You can contact FASEB for the reports of the SCOGS committee.*" We of course already had obtained the final reports referred to in Michael's reply. The SCOGS report is, of course, published and in the public domain. At our GRAS pre-notification meeting, FDA thought they would be able to find archived copies of these study reports. Unfortunately, these could not be located.

4. For each of the studies discussed in section 6.1.2., the notifier does not provide an abbreviated reference, even though the full primary references (#36 and 37) for these studies are available from the References section. Please clearly identify the reference number for the studies that the notifier discusses in section 6.1.2.

> The GRAS discussed several toxicological studies on the structurally similar compound, methyl hesperidin (which they stated is 99% similar to hesperidin according to Tanimoto's structure similarity). Methyl hesperidin was found to be non-toxic and non-carcinogenic in mice when given at up to 5% in the diet for 13 to 96 weeks. A 13-week dose range-finding study of the compound also showed no toxic effects. The NOAEL determined for both the 13-week[*36*] and 96-week[*37*] studies was 5% in the diet, the highest dose level tested. The NOAEL in the 96-week study was stated to correspond to intake levels of 7500 mg/kg bw/day for males and 8,600 mg/kg bw/day for females. The notifiers calculated an Acceptable Daily Intake (ADI) level for hesperidin of 75 mg/kg bw/day, by using the methyl-hesperidin NOAEL of 7500 mg/kg bw/day and a 100-fold safety factor. They stated their hesperidin exposure estimate of 8 mg/kg bw/day, plus their background exposure estimate from oranges in the diet of 1 mg/kg bw/day, was well below their calculated ADI of 75 mg/kg bw/day.

Response:
36. *Kawabe M, Tamano S, et al. Subchronic toxicity study of methyl*

hesperidin in mice. Toxicol Lett. 1993;69(1):37-44
37. *Kurata Y, Fukushima S, et al. Carcinogenicity study of methyl hesperidin in B6C3F1 mice. Food Chem Toxicol. 1990;28(9):613-8*

5. On page 28, the notifier states "A reproductive study, published in 1954 by Palmer and Patterson …". FDA notes that this is an unpublished report. Please confirm.

Response: Yes, it appears that a copy of this report was submitted to LSRO, but we were not successful in finding a published version of the report/study upon contacting LSRO.

6. In support of your safety determination, please provide a brief discussion of the following studies:
a) Li, P., Wang, S., Guan, X., Cen, X., Hu, C., Peng, W., ... & Su, W. (2014). Six months chronic toxicological evaluation of naringin in Sprague–Dawley rats. Food and Chemical Toxicology, 66, 65−75.
b) Li, P., Wang, S., Guan, X., Liu, B., Wang, Y., Xu, K., ... & Zhang, K. (2013). Acute and 13 weeks subchronic toxicological evaluation of naringin in Sprague-Dawley rats. Food and Chemical Toxicology, 60, 1−9.

Response: Available data from studies of naringin can be noted as a relevant contribution towards knowledge of narirutin by way of their structural similarity and common aglycone; narirutin is the naringenin aglycone bound to rutinose, while naringin is the naringenin aglycone bound to neohesperidose, which differs from rutinose only in its intersaccharide linkages.[1] Both narirutin and naringin have the same molecular weight. To reiterate from section 6.2 of the notification (Pharmacokinetics of Hesperidin and Narirutin), the glycoside narirutin is cleaved by colonic bacteria to release the aglycone naringenin for absorption in the large intestine. Since the same metabolic fate awaits naringin upon its consumption (hydrolyzation to naringenin in the gut, with relatively low bioavailability and rapid excretion), we believe safety data for naringin is supportive of demonstrating the safety of narirutin. Please find the brief discussions of the two naringin studies by Li et al. below.

The acute, subchronic (13-week) and chronic (6-month) oral toxicity of naringin (extracted from *Citrus grandis* Tomentosa) was assessed in Sprague-Dawley rats. In the acute study,[2] six rats/sex/group were given naringin (16 g/kg) or sterile saline (control). Animals were observed for the onset of any toxic signs immediately after administration and once daily thereafter for 14 days. No deaths occurred, and no clinical signs were observed. Normal body weight gains and food intakes occurred in both groups. Hematology, clinical chemistry and macroscopic examination of organs were similar between groups. Activated partial thromboplastin time in the naringin treatment group was significantly longer than that of the control group but stayed within the normal reference range. The LD_{50} was considered greater than 16 g/kg.

For the 13-week and 6-month studies, 176 rats were randomly assigned to one of four groups (22 rats/sex/group). The dose groups were 0 (sterile water), 50 (low), 250 (mid) and 1250 (high) mg/kg bw/day of naringin given by gavage, with a dose frequency of 6-days per week. In each group, 12, 8, 16 and 8 rats were assigned to the 13-week study, 13-week recovery, 6-month study and 6-month recovery respectively. Recovery periods were one-month long.

In the 13-week study[2], no mortality or abnormal clinical signs related to treatment were observed. Functional behavioral results were comparable between groups. No ophthalmological abnormalities were observed. Statistically significant decreased mean body weight in the 250 and 1250 mg/kg bw/day groups were noted at some observation points compared to controls (after the 6th week in females and after the 11th week in males for the high dose group, and in the 7th, 8th, 12th and 13th weeks in females for the mid dose group). In females, food consumption in the high dose group was less than controls in the 5th and 9th weeks. The decreased body weight compared to controls was not associated with other clinical signs or indications of pathology, and the decrease in food consumption may have contributed to the weight loss. With regard to hematology, the only finding was an increased lymphocyte percentage in the high dose group compared to controls, which was still within normal physiological ranges. With regard to clinical chemistry, urea was decreased in the high dose group (which may have been related to the decrease in food intake), and total bilirubin levels in all dose groups were decreased compared to controls but remained within normal ranges. No changes were noted in dihydrotestosterone (DHT) or estradiol (E2) in the groups. With regard to organ weights, in females, the absolute heart and lung weights were significantly decreased in the high dose group. Brain to body weight ratios were increased in the mid and high dose groups. Heart to brain ratios in the high dose group and lung to brain ratios in the mid and high female dose groups were decreased. All findings related to organ weights in the study remained within normal laboratory ranges and were not sex or dose-related. Macroscopic examination revealed liver spots in one male rat of the mid dose group, and sparse hair on the back of the neck of one female in the high dose group. Histopathological observations revealed various minimally severe lesions in the treatment and control groups, and all were considered spontaneous and/or incidental in nature and not related to naringin treatment. The NOAEL was concluded to be 1250 mg/kg bw/day, the highest dose tested.

In the 6-month study,[3] two deaths occurred (one female rat in the 50 mg/kg bw/day group on day 76, and one female in the 1250 mg/kg bw/day group on day 24); both deaths were considered to be due to improper intragastric administration based on macroscopic and histopathological examinations. No deaths or clinical signs related to naringin treatment were noted. All functional behavioral results were comparative to controls, and no ophthalmological abnormalities occurred in the study. From the second month to the sixth month, slight hair loss was noted on some skin areas including the necks in three female control rats, the necks in one female and one male in the low dose group, the necks ears and/or around the eyes in four females and one male from the mid dose group, and the backs, necks, chests, abdomens and/or femoral regions in three females and two males from the high dose group. The hair loss gradually returned to normal in the recovery period. The authors noted that in an unpublished study they performed in Beagle dogs, no hair loss occurred. As the hair loss in rats occurred in controls as well as treated groups and was slight and reversible, it did not appear to be a toxicologically significant effect of naringin.

Mean body weights of the high dose females were decreased weeks 7–13, 17–19 21 and 26 compared to controls; high dose males were decreased weeks 12–26; and mid dose females were decreased weeks 7, 8, 12 and 13. Body weights were increased compared to controls in the low dose group females weeks 28–30. Food consumption was also decreased in high dose females weeks 5, 13, 15–16, 21–22 and 24 compared to controls, although was more than the controls at

week 18. Food consumption in males of mid and high dose groups was more than the controls week 10. Overall the body weights were not associated with clinical signs or abnormal pathology and agreed with results in the 13-week study, and the decrease in food consumption may have played a role.

All hematology and clinical chemistry findings were considered toxicologically irrelevant because they were small in magnitude, within normal ranges, and were not dose-related or reflected by any changes in other related clinical parameters. No changes in DHT or E2 were noted during the treatment period, although at the end of the recovery period, DHT levels in the mid dose group were significantly decreased. As the change was not accompanied by corresponding clinical or histopathological changes, it was considered to be normal physiological variance unrelated to treatment.
As in the 13-week study, various differences occurred in treatment group organ weights/ratios compared to controls, but the changes were not sex- or dose-related, were within the normal laboratory ranges, and/or were not supported by any other consistent or toxicologically significant changes in other parameters and were judged to be of little toxicological significance. Similarly, various lesions were noted histopathologically in control and treatment groups, but all were considered spontaneous and/or incidental in nature and not relevant to naringin treatment. The NOAEL for naringin in the 6-month study was also considered to be 1250 mg/kg bw/day, the highest dose tested.

In conclusion, the LD_{50} for naringin was considered to be greater than 16 g/kg in the acute study, and the NOAEL for naringin in both the subchronic and chronic studies was 1250 mg/kg bw/day, the highest dose tested. As mentioned, narirutin and naringin are closely related compounds comprised of the same aglycone and slightly different sugar moieties and have the same molecular weight, thus their toxicological profiles can be considered very relevant to each other. The 90^{th} percentile exposure estimate for Orange Extract was determined to be 12.8 mg/kg bw/day. The specification for narirutin in the Orange Extract is up to 8%, hence the maximum exposure to narirutin from the extract will be 1.02 mg/kg bw/day (12.8 x 0.08). Using the naringin NOAEL of 1250 mg/kg bw/day and dividing it by the exposure estimate for narirutin of 1.02 mg/kg bw/day, a margin of safety for narirutin can be estimated as 1225, which is higher than the usual expected margin of safety for a food ingredient of 100 (per 21 CFR §170.22) and suggests that the intended use level of narirutin in Orange Extract is reasonably certain to be safe.

1. Satterfield M and Brodbelt JS. Structural characterization of flavonoid glycosides by collisionally activated dissociation of metal complexes. *J Am Soc Mass Spectrom*. 2001;12(5):537-49
2. Li P, Wang S, et al. Acute and 13 weeks subchronic toxicological evaluation of naringin in Sprague-Dawley rats. *Food Chem Toxicol*. 2013;60:1-9
3. Li P, Wang S, et al. Six months chronic toxicological evaluation of naringin in Sprague-Dawley rats. *Food Chem Toxicol*. 2014;66:65-75

From:	John Endres
To:	Kolanos, Renata
Cc:	Amy Clewell
Subject:	Re: REGARDING: GRAS Notice GRN No. 000796
Date:	Tuesday, February 05, 2019 8:58:44 PM
Attachments:	image003.png Ferrer--Orange Extract GRN--Response to FDA 05Feb2019.pdf

---

Hi Renate,

Thanks for the question. Please see our attachment that we think answers what was requested. Please advise. Let me know if you would like to discuss further.

Thanks very much.

Best Regards,
John

John R. Endres, ND
Chief Scientific Officer
AIBMR Life Sciences, Inc.
Ph. (253) 286-2888
www.aibmr.com
www.toxicoop.com

AIBMR
Life Sciences, Inc.

February 5, 2019

ATTN: Renata Kolanos, PhD
Consumer Safety Officer
Renata.Kolanos@fda.hhs.gov

Re: GRN 796 Literature Search Dates

Dear Renata,

The literature search performed for GRN 796 Orange Extract was through May, 2018, and pertinent information related to the safety of Orange Extract was included in the notice. There was no information uncovered that contradicts or was inconsistent with the determination that Orange Extract is GRAS.

Please let us know if you need any additional information.

Sincerely,

John Endres, ND
Chief Scientific Officer

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