

GRAS Notice (GRN) No. 658

<http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm>

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ORIGINAL SUBMISSION

**Notice to the US Food and Drug Administration  
that the use of Vancitrix™, a glycerin Citrus  
Extract, is Generally Recognized as Safe**

Submitted and Prepared by the Notifier:

GRN 000658

Chemie Research & Manufacturing, Co., Inc.

RECEIVED

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18 March 2015 (Original submission)

OFFICE OF  
FOOD ADDITIVE SAFETY

07 June 2016 (Revised submission)

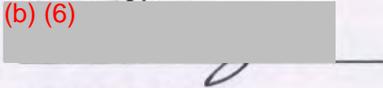
THOMAS WRIGHT

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**GRAS Exemption Claim**

Chemie Research & Manufacturing, Co., Inc. (the notifier) has determined that Vancitrix™ grapefruit extract, hereafter referred to as Vancitrix™, is Generally Recognized as Safe (GRAS) for its intended use, consistent with section 201 (s) of the Federal Food, Drug and Cosmetic Act. The determination has been made based on experience of common use in food as well as scientific procedures, and therefore the use of Vancitrix™ grapefruit extract, for its intended purpose is exempt from the requirement of pre-market approval.

(b) (6) 

7-June-2016

Thomas R. Wright

Date

Chemist, Chemie Research & Manufacturing. Co., Inc.

**Name and Address of Notifier**

Thomas R. Wright

Chemie Research & Manufacturing. Co., Inc.

160 Concord Drive

Casselberry, FL. 32707

USA

**Common or Usual Name**

Vancitrix™ is an organic glycerin extract from organic *Citrus X paradisi*.

**Conditions of Use**

Vancitrix™ is intended for use as an ingredient at a concentration of up to 125mLs / L (V/V) / serving in all food categories including beverages and dietary supplements, where standards of identity allow, except that it is not intended for use in infant formula or in food products that are regulated by the United States Department of Agriculture (USDA). Vancitrix™ is intended to be used as a supplemental / additive source for ascorbic acid and citric acid primarily, with additional antimicrobial / antioxidant benefits in some food products (see microbial assay, page 11). As a food additive, Vancitrix™ would fall under two types of ingredient classifications. The first being as a preservative where ingredients include; ascorbic acid and citric acid. Additional preservative qualities are derived from antioxidant benefits from ascorbic acid, citric acid, naringin and other bioflavonoids. The second type of ingredient is as a nutrient based on the additional vitamin C. The purpose of adding Vancitrix™ to food would be:

1. To Maintain or improve safety and freshness – one example of preservatives are antioxidants.
2. To improve or maintain nutritional value – this would be an example of how ascorbic acid and citric acid could be used as a nutritional supplement.

### **Basis for GRAS Determination**

Experience based on common use in food of all ingredients that compose Vancitrix™, as well as scientific procedures are the basis for this GRAS determination. Please see current regulatory status on page 14 for more details.

### **Data / Information Availability Statement**

The data and the information that serve as the basis for this GRAS determination will be available for review and copying at reasonable times at the office of Chemie Research & Manufacturing, Co., Inc. 160 Concord Drive, Casselberry, FL. 32707 or will be sent to FDA upon request.

### **Characterization**

Vancitrix™ is formulated based on a glycerin extract of organic grapefruit which is Chemie Research and Manufacturing, Co., Inc.'s certified organic proprietary glycerin grapefruit extract. The grapefruit extract is prepared from organic grapefruit grown and harvested in Florida, USA. One GRAS citrus species is used in the manufacturing of Vancitrix™, which is *Citrus X Paradisi*.

21 CFR 101.44 states that grapefruit is among the 20 most frequently consumed raw fruits. Grapefruit, specifically *Citrus Paradisi Macf* is listed in both: 21 CFR 182.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are Generally Recognized As Safe for their intended use, within the meaning of section 409 of the Act. 21 CFR 582.20 Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) that are generally recognized as safe for their intended use, within the meaning of section 409 of the Act.

As will be further discussed, Vancitrix™ consists of organic certified vegetable sourced glycerin (palm – free), grapefruit extract (glycerin extract using organic certified vegetable sourced glycerin and organic certified grapefruit, *Citrus X Paradisi*), non-organic ascorbic acid, non-organic lactic acid, non-organic naringin and non-organic citric acid.

The organic grapefruit are harvested and juiced at a local organic certified grower in Central Florida. The peel, rind, rag and seeds are then moved to another facility, which is also organic certified, for drying. These dried remnants are then added to organic vegetable glycerin as heat and pressure are applied to create the extract. The resulting extract is added to more organic vegetable glycerin along with ascorbic acid, lactic acid, naringin and citric acid. All of these ingredients are food grade and non-GMO. The product is tested on a per batch basis through a well-established quality control program to confirm the product's physical and chemical characterization. Certificates of analysis are available upon request detailing instrumentation used as well as value ranges.

Consumption of citrus fruits is known to be beneficial to human health (Baghurst 2003; McIndoo, 2012). The polyphenolic components of citrus fruits have been linked to various health promoting properties. Citrus fruits are high in antioxidants, such as vitamin C and flavonoids, which provide protection against harmful free radical species and oxidative stress (Jayaprakasha et al. 2008).<sup>1</sup>

## Chemical Composition

Vancitrix™ is a water soluble, proprietary glycerin grapefruit extract prepared from locally grown organic grapefruit. The product is a non-volatile, non-flammable, non-toxic transparent liquid with a Gardner color range of 8 – 12. The specific gravity range is 1.10 – 1.35 g/mL, and a pH range of 1.5 – 3.5. Approximately 2.65% ascorbic acid is added to the final product. Additional ascorbic acid that is determined via Metro Ohm Easy Ox DPI titration is attributed to ascorbic acid added as per the formulation and in the grapefruit extract itself. Active bioflavonoids that are prevalent in the grapefruit extract are naringin and narirutin.

## Organic Certification

The extract used to make Vancitrix™ is certified through Quality Certification Services under the US National Organic Program 7 CFR Part 205. QCS Entity ID: 1783P. All ingredients used to include those that are not certified organic are non-GMO and food grade. GMP is adhered to in all stages of production.

### Certified Products

#### Organic

Product	ID Mark	Date Added	Compliance
DF-100 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	NOP
DF-100 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	Japan Export Arrangement
DF-100 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	Taiwan Export Arrangement
DF-100 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	US-Canada Equivalency
DF-100 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	US-EU Equivalency
P-50 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	NOP
P-50 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	Japan Export Arrangement
P-50 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	Taiwan Export Arrangement
P-50 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	US-Canada Equivalency
P-50 Organic Grapefruit Extract-Liquid	Chemie Research & Manufacturing Co., Inc.	3/10/14	US-EU Equivalency

## **Manufacturing and Production**

### **Company Overview**

Central Florida based Chemie Research & Manufacturing, Co., Inc. has been developing grapefruit seed extract for use in cosmetics for more than 40 years since the inventor of grapefruit seed extract, Dr. Jakob Harich, founded the company. In 2013 an organic certified dietary supplement was developed. This GRAS notification is applicable to the products made using the organic extract.

### **Raw Materials**

Organically grown grapefruit (*Citrus X paradisi*) from a certified grower in Central Florida. Additional raw materials include:

Organic glycerin: CAS # 56-81-5

Citrus X paradisi Ex (from organic grapefruit and organic glycerin): CAS # 1586019-34-2

Citric acid: CAS #77-92-9

Ascorbic acid: CAS #50-81-5

Lactic acid: CAS #79-33-4

Naringin: CAS #10236-47-2

### **Manufacturing**

Chemie Research & Manufacturing, Co., Inc. uses only certified organic grapefruit for the Vancitrix™ product. The grapefruit are juiced and the remainder of the fruit is what is used for the production. The peel, rind, rag and remaining seeds are shipped to a separate organic certified facility for drying yielding grapefruit “flakes” before being shipped to Chemie Research & Manufacturing, Co., Inc. Figure 1 outlines the manufacturing process of Vancitrix™. The grapefruit flakes are placed in an extraction chamber where organic certified glycerin is added. Heat and pressure are applied to yield a dark, viscous liquid extract. The extract is then filtered to remove any remaining solids. In a separate production tank more of the organic glycerin is added as well as ascorbic acid, citric acid, lactic acid and naringin. The solids are allowed to dissolve before the organic grapefruit extract is added. This mixture is heated and agitated to a specific temperature and for a specific amount of time. A sample is pulled per batch and tested through the quality control protocol. Instrumentation utilized in the quality control protocol include Perkin Elmer Clarus 500 GC/MS, Perkin Elmer Spectrum One FTIR, Metrohm EasyOx autotitrator(DPI), Accumet pH meter and Gardner color meter.

## Flow Chart

### Vancitrix™ – Grapefruit Extract

1. Selection of CERTIFIED ORGANIC grapefruit flakes
2. Weighing and measuring of ingredients
3. First step production – Extraction tank (addition of organic glycerin)
4. Active ingredients extraction by glycerin maceration process
5. Pressed / filtered for solids separation
6. Second step production – Production tank (addition of organic glycerin)
7. Addition of ascorbic acid, citric acid, lactic acid and naringin
8. Mix and dissolve solids – Addition of grapefruit extract
9. Pull sample for Quality control
10. Quality Control stage *
11. Add ingredients if necessary (ascorbic acid, citric acid, extract), mix
12. Quality control approval *
13. Bulk packaging
14. Quarantine Stage (Organic protocol)
15. Equipment cleaning (Organic procedure)
16. Traceability – samples per batch are stored for 3 years minimum
17. Metal detection done by outside lab via ICP – periodically
18. Packing
19. Finished product labeling
20. Equipment cleaning (Organic procedure)
21. Finished product analysis
22. Finished product release
23. Storage and distribution

**Figure 1.** Manufacturing Process Flow Diagram for Vancitrix™ Grapefruit Extract

- Step 10 and 12 represents Critical Control Points (CCP) in the HACCP plan.

## Specifications and Batch Analysis

### Specifications and Quality Control

Production consistency of Vancitrix™ Grapefruit Extract batches is accomplished through a combination of AOAC approved analytical methods and incorporated automated analytical methods.

Parameter	Specification	Method	Batch Number		
			OP-1	OP-2	OP-3
Quality Control			OP-1	OP-2	OP-3
Liquid Appearance	6 - 12	Gardner Scale reader	8	8	7
pH	1.5 – 3.5	AOAC 973.41	2.53	2.62	2.55
Specific gravity	1.10 – 1.35	AOAC 945.06	1.25	1.23	1.26
Ascorbic acid	4% Min.	AOAC 967.21	15.0	12.5	17.9
Water content	0 – 4.0%	KF Titrator	1.21	1.11	1.19
Infrared Identity	Comparable spectra	KBr plate PE FTIR scan	PASS	PASS	PASS
Materials screening	Comparable spectra	In house method GC/MS *	PASS	PASS	PASS
Lead	</= MDL	EPA 6010C	PASS	PASS	PASS

Note: AOAC Methods acquired via [www.aoac.org](http://www.aoac.org)

\*In house GC/MS method developed via research done by JPT Analytical Associates, Gainesville, FL.

### Ascorbic acid, Citric acid, Naringin and other Flavonoids

Testing was conducted by an outside laboratory: JPT Analytical Associates LLC, Gainesville, Florida. Complete report is available to the FDA upon request. Initial testing was performed on three (3) separate formulation samples.

#### Summary of report:

All of the compounds were detected, identified and quantified using Liquid Chromatography in combination with tandem mass spectrometry (LC/MS/MS). Optimum chromatographic separation, sensitivity and selectivity were obtained using reverse phase gradient LC conditions and negative ion electrospray ionization ((-) ESI MS) mass spectrometric conditions.

Compounds were identified by comparison of their chromatographic retention times, parent ion mass spectra and MS/MS fragmentation patterns with those of authentic standards of ascorbic acid, citric acid and naringin. One chromatographic peak displayed a parent ion and fragmentation pattern similar to those of the naringin standard, permitting its identification as the bioflavonoid narirutin, an isomer of naringin. Other peaks displayed spectra indicative of flavonoids, but could not be identified precisely. The intensity of the naringin peak was roughly 1000-fold greater than those of narirutin and the other flavonoids.

Concentrations of ascorbic acid, citric acid and naringin were calculated from their chromatographic peak areas using calibration curves generated from peak areas obtained for solutions of authentic standards. Concentrations of narirutin were calculated using the calibration curve generated for naringin.

Based on the analysis described above, concentrations in micrograms per milligram of product (parts-per-thousand) were found to be:

<u>Sample</u>	<u>Ascorbic acid</u>	<u>Citric acid</u>	<u>Naringin</u>	<u>Narirutin</u>
OP-1	15.0	31.8	14.1	0.0179
OP-2	12.5	24.4	13.3	0.0214
OP-3	17.9	34.1	13.4	0.0071

### Screening for Pesticides / Bactericides

A standard screen was done for a total of 57 pesticides and 2 types of bactericides:

Thirteen Organochlorine (OC) insecticides:

Six Organophosphorus (OP) insecticides:

Eleven Carbamate insecticides:

Twenty-seven compounds in a variety of chemical classes that are used as insecticides, herbicides and fungicides:

None of the 57 compounds were detected in the sample. Screening for Benzethonium chloride (BEC) and Benzalkonium chloride (BAC) were performed by LC/MS/MS. No Quaternary Ammonium compounds were detected.

### Heavy Metal Analysis

#### Metals by EPA 6000/7000 Series Methods

<u>Analyte [CAS Number]</u>	<u>Result</u>	<u>Flag</u>	<u>Units</u>	<u>DF</u>	<u>MDL</u>	<u>PQL</u>	<u>Method</u>	<u>Analyzed</u>	<u>NELAC</u>
Antimony [7440-36-0]	0.790	U	mg/kg wet	1	0.790	1.61	EPA 6010C	4/7/11	E82277
Arsenic [7440-38-2]	0.629	U	mg/kg wet	1	0.629	0.806	EPA 6010C	4/7/11	E82277
Beryllium [7440-41-7]	0.0115	U	mg/kg wet	1	0.0115	0.0806	EPA 6010C	4/7/11	E82277
Cadmium [7440-43-9]	0.0226	U	mg/kg wet	1	0.0226	0.0806	EPA 6010C	4/7/11	E82277
Chromium [7440-47-3]	0.0806	U	mg/kg wet	1	0.0806	0.806	EPA 6010C	4/7/11	E82277
Copper [7440-50-8]	0.258	U	mg/kg wet	1	0.258	0.806	EPA 6010C	4/7/11	E82277
Lead [7439-92-1]	0.387	U	mg/kg wet	1	0.387	0.806	EPA 6010C	4/7/11	E82277
Mercury [7439-97-6]	0.0800	U	mg/kg wet	5	0.0800	0.120	EPA 7471B	4/7/11	E82277
Nickel [7440-02-0]	0.129	U	mg/kg wet	1	0.129	4.03	EPA 6010C	4/7/11	E82277
Selenium [7782-49-2]	0.774	U	mg/kg wet	1	0.774	0.806	EPA 6010C	4/7/11	E82277
Silver [7440-22-4]	0.102	U	mg/kg wet	1	0.102	0.806	EPA 6010C	4/7/11	E82277
Thallium [7440-28-0]	0.516	U	mg/kg wet	1	0.516	0.806	EPA 6010C	4/7/11	E82277
Zinc [7440-66-6]	1.56	U	mg/kg wet	1	0.435	4.03	EPA 6010C	4/7/11	E82277

## **Minimum Inhibitory Concentration (MIC) of Organic GSE Products against Four Selected Microorganisms.**

Testing provided by ABC Research Laboratories in Gainesville, Florida.

### Test Products and Materials:

The client (Chemie Research & MFG, Co., Inc.) provided sufficient quantity (ca. 50 mL) of three organic GSE product formulas. Organic Grapefruit Seed Extract (GSE) product codes were OP-1, OP-2, and OP-3.

### Test Microorganisms:

The following four organisms were used in this study: Generic *E. coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 9027), *Aspergillus brasiliensis* (ATCC 16404), and *Candida albicans* (ATCC 10231).

### MIC Procedure:

MIC (minimum inhibitory concentration) assays for the organic GSE products were conducted separately for each product against each selected microorganism using the "broth macro-dilution" procedure for antibiotic susceptibility testing per NCCLS/CLSI methods (National Committee for Clinical Laboratory Standards, now referred to as Clinical and Laboratory Standards Institute). The inoculum for each microorganism was prepared and the MIC assay conducted according to respective culture methods described by NCCLS (M7-A5, 2000).

### Results and Discussion:

The formulation making up OP-1 turned out to have the best MIC values. Therefore, the OP-1 formulation is the procedure used for Vancitrix™.

The MIC values were 6.25 %, 6.25 %, 50 % and 25% for *E. coli*, *P. aeruginosa*, *A. brasiliensis*, and *C. albicans* respectively.

These MIC values are to be referred to when considering concentration for specific applications.

**Microbial Assay**

Microbiological testing is conducted per batch of Vancitrix™ utilizing disk diffusion assay protocol. Additionally, verification testing is conducted by ABC Research Labs ([www.abcr.com](http://www.abcr.com)) according to USP methods 51 and 1227. Initial verification testing was done to determine MIC for the original formulation of Vancitrix™. Log-unit changes after 14 and 28 days were calculated to determine compliance with USP 51 acceptance criteria. USP 51 acceptance criteria for Category 3 products (i.e., Oral products other than antacids, made with aqueous bases or vehicles) are presented in the following table (note: no increase is defined as not more than 0.5 log<sub>10</sub> unit higher than the previous value measured):

**Category 3 Products**

Bacteria:	Not less than 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeasts and Mold:	No increase from the initial calculated count at 14 and 28 days.

Previous MIC testing determined that a starting concentration of 6.25% would be recommended. A 3.0% concentration was also tested.

Vancitrix™ 3.0%:

E. coli, P. aeruginosa, and S. aureus were undetectable in 3% Vancitrix™ after 14 days of storage at 20-25° F (i.e., <10 CFU/g), and remained undetectable after 28 days of storage. The 3% Vancitrix™ met acceptance criteria per USP 51 as presented below in Table 1.

**Table 1. USP 51 Testing for Vancitrix™ Grapefruit Extract, 3% Concentration**

Organism		Storage Time (days) and Microbial Challenge Results				
		0	14		28	
<i>Escherichia coli</i> (ATCC 8739)	CFU/g	38,000,000	<10	Pass	<10	Pass
	Log <sub>10</sub> CFU/g	7.58	<1.00		<1.00	
<i>Pseudomonas aeruginosa</i> (ATCC 9027)	CFU/g	25,000,000	<10	Pass	<10	Pass
	Log <sub>10</sub> CFU/g	7.40	<1.00		<1.00	
<i>Staphylococcus aureus</i> (ATCC 6538)	CFU/g	28,000,000	<10	Pass	<10	Pass
	Log <sub>10</sub> CFU/g	7.45	<1.00		<1.00	
<i>Candida albicans</i> (ATCC 10231)	CFU/g	2,000,000	870,000	Pass	520,000	Pass
	Log <sub>10</sub> CFU/g	6.30	5.94		5.72	
<i>Aspergillus brasiliensis</i> (ATCC 16404)	CFU/g	19,000,000	22,000	Pass	3,600	Pass
	Log <sub>10</sub> CFU/g	7.28	4.34		3.56	

## History of Consumption

The grapefruit was known as the *shaddock* or *shattuck* until the 19<sup>th</sup> century. Its current name alludes to clusters of the fruit on the tree, which often appear similar to grapes. Botanically, it was not distinguished from the pomelo until the 1830s, when it was given the name *Citrus paradisi*. Its true origins were not determined until the late 1940s. This led to the official name being altered to *Citrus x paradisi*, the “x” identifying its hybrid origin.

## Production

The United States is the top producer of grapefruit and pomelo followed by China and South Africa.

### Top Grapefruit (including pomelos) producers – 2007

<u>Country</u>	<u>Production (metric tons)</u>
United States	1,580,000
People’s Republic of China	547,000
South Africa	430,000
Worldwide	5,060,000

Reference: <http://en.wikipedia.org/wiki/grapefruit>

## **Safety Assessment**

### **Toxicological Studies**

Historically, there have been no safety concerns associated with the consumption of *C. x Paradisi*, and as such, safety assessments are absent from the public domain despite widespread consumption of fruit from this species. The primary concern has to do with drug interactions, which have been examined and the results are listed below.

### **Drug Interactions**

Grapefruit can have a number of interactions with several drugs, often changing the potency of the compounds. This is largely due to a number of polyphenolic compounds as well as furanocoumarins (which is primarily located in the juice). We had a sample of Vancitrix™ labeled as DF-100 SDI-1 in June of 2013. Based on published data (J.A. Manthey and B.S. Buslig, "Distribution of Furanocoumarin in Grapefruit Juice Fractions", *J. Agric Food Chem.*, **2005**, 53, 5158-5163.) Analysis was performed by JPT Analytical Associates, LLC. In Gainesville, Florida utilizing a modification of published procedures based on HPLC in combination with positive ion electrospray ionization (+ESI). The report (available to the FDA upon request) describes the results of analysis of three samples of Grapefruit seed extract products from Chemie Research & MFG, Co., Inc. (one of which was labeled DF-100 SDI-1 for testing purposes only) for two furanocoumarins, Bergamottin (BG) and 6'7' – dihydroxygergamottin (DHB).

### Conclusions:

Based on the amounts of furanocoumarin analytes in grapefruit juice and fractions thereof, for every 1 furanocoumarin analyte in the GSE, there are at least 1,000 in juice or fractions of juice.

## Current Regulatory Status

### Regulatory Status of Citrus Fruit

The fruit used for Vancitrix™ is *C. Paradisi* with additional Naringin added to the formulation (source is *C. Paradisi*). Both of these components are GRAS and listed in 21 CFR 182.20.

### Regulatory Status of Additional Vancitrix™ Components

Citric acid: (CAS #77929) is considered FDA GRAS for use in foods with no limitations other than good manufacturing practice, in accordance with 21 CFR 184.1033 21 CFR 184.1(b)(1).

Vegetable glycerin: (CAS #56-81-5) is FDA GRAS in accordance with 21 CFR 182.1320, as a multiple purpose food substance that is generally recognized as safe when used in accordance with good manufacturing practice.

Ascorbic acid: (CAS #50-81-7) (Vitamin C) is considered FDA GRAS in accordance with 21 CFR 182.8013 as a nutrient in foods when used in accordance with good manufacturing practice.

Lactic acid: (CAS #79-33-4) is FDA GRAS for use in foods with no limitations other than good manufacturing practice, in accordance with 21 CFR 184.1(b)(1).

Naringin: (CAS #10236-47-2) is FDA GRAS for its intended use within the meaning of section 409 of 21 CFR 182.20.

### Intended Use

Vancitrix™ is intended for use as an ingredient in all food categories where standards of identity allow, except that it is not intended for use in infant formula or in food products that are regulated by the USDA. It is intended to be used as a supplemental / additive source for ascorbic acid and citric acid primarily, with additional antimicrobial / antioxidant benefits in some food products (see microbial assay, page 11). As a food additive, Vancitrix™ would fall under the two types of ingredients ([www.FDA.gov/food/ingredientspackagingLabeling/FoodAdditiveIngredients](http://www.FDA.gov/food/ingredientspackagingLabeling/FoodAdditiveIngredients)). The first being as a preservative where ingredients include; ascorbic acid and citric acid. Additional preservative qualities are derived from antioxidant benefits from ascorbic acid, citric acid, naringin and other bioflavonoids. The second type of ingredient is as a nutrient based on the additional vitamin C. The purpose of adding Vancitrix™ to foods would be:

1. To Maintain or Improve Safety and Freshness- one example of preservatives are antioxidants.
2. To improve or maintain nutritional value- this would be an example of how ascorbic acid and citric acid could be used as a nutritional supplement.

## Estimated Daily Intake (EDI)

The ratio of ascorbic acid to citric acid is approximately 1:2. The RDA of ascorbic acid is typically 90 mg / day for adult men and women not to exceed 2,000 mg / day. Independent testing has determined that Vancitrix™ at full strength contains approximately 15,000 ppm ascorbic acid (on average) and 30,000 ppm citric acid (on average). The report has the values listed in parts-per-thousand (ppt). By using a 1:8 dilution factor, the dosage used would be 125 mLs per Liter to yield an approximate concentration of ascorbic acid at 1875 mg / L (Maximum exposure). Vancitrix™ is intended to be used most frequently at a concentration of 500 ppm, with a maximum concentration of 1250 ppm. The estimated daily intake (EDI) or exposure to Vancitrix™ was calculated based on data related to the maximum amount of food consumed daily by Americans by weight. It is reasonable to consider daily food intake data when calculating the daily intake of Vancitrix™ by calculating 1250 ppm of total food intake (0.125%). The calculations lead to a highly conservative estimation of daily consumption, which is likely much higher than the amount that would be consumed by the majority of consumers.

The mean total food intake by mass from major food groups (edible and uncooked), according to the U.S. Environmental Protection Agency (EPA) 2011 Exposure Factors Handbook (Chapter 14, Table 14-5) are listed in Table 2 (EPA 2011). Data was collected from surveying 20,000 individuals on two non-consecutive days. If Vancitrix™ were added to all food categories listed in the EPA report at 1250 ppm (.1250%) per day, then an individual aged  $\geq 20$  years, weighing 70 kg and consuming 1050 g of food (15 g/kg bw mean food consumption x 70 kg individual = 1050 g) from major food groups (edible and uncooked) on average per day would be exposed to a maximum of 1.3 g of Vancitrix™ (1050 g x 0.125% = 1.3 g). This value would be approximately 2.5 g of Vancitrix™ for individuals in the 95<sup>th</sup> percentile group (individuals > 20 years of age, weighing 70 kg and consuming 28 g food/kg bw/d will consume 28 g x 70 kg bw x 0.125% = 2.45 g of Vancitrix™ per day). For children aged 3 – 6 years, exposure for the 95<sup>th</sup> percentile would also be approximately 2.5 g (102 g food/kg bw x 20 kg bw x 0.125%).

**Table 2:** Daily Vancitrix™ Exposure based on EPA data, if it were added to all foods consumed.

Age Group	Per Capita Total Food Intake from Major Food Groups (Edible and Uncooked) (g/kg bw)			Exposure to Vancitrix™ if added to all foods (addition level of 1250 ppm) Based on the Per Capita Total Food Intake from Major Food Groups (Edible and Uncooked) (g/kg bw)		
	Mean	10 <sup>th</sup> %	95 <sup>th</sup> %	Mean	10 <sup>th</sup> %	95 <sup>th</sup> %
3 to <6	61	34	102	0.0763	0.043	0.128
6 to <11	40	21	70	0.05	0.026	0.088
11 to <16	24	11	45	0.03	0.014	0.056
16 to <21	18	8	35	0.023	0.01	0.044
>20	15	8	28	0.019	0.01	0.035

Alternatively, using data obtained from the 2012 Statistical Abstract published by the US Census Bureau, under Section 3 entitled Health and Nutrition, and taking data from Tables 217 and 218, the amount of Vancitrix™ likely to be consumed per day was calculated to be approximately 2.2 – 2.6 g based on consumption data for 1980 – 2009 (US Census Bureau 2012). The majority of the food consumption data was calculated based on beginning stocks, domestic production, and imports; from which exports, nonfood use, and ending stocks were subtracted. The census data was based on all major food categories. Food intake from these categories ranged from 1,773 – 2,036 g/day, which amounts to approximately 2.2 – 2.6 g of Vancitrix™ per day at a level of 1250 ppm or 0.125%.

The US Census Bureau 2012 Statistical Abstract is based on USDA regulated categories of foods. However, Vancitrix™ is not intended to be added to USDA regulated categories of food under this GRAS notification. Cost limitations and standards of identity would likely prohibit the addition of this ingredient to any food groups. Additionally, the average intended use of Vancitrix™ is at a significantly lower concentration (500 ppm), as compared to the maximum intended use of 1250 ppm which was used in the previous exposure calculations.

### **General Recognition**

The information that provides the basis for this GRAS determination by experience based on common use in food is available in the public domain. The reference section of this notification will document in a concise order the references that have been used and noted throughout this document. There is no data that we are aware of that would argue against the components of Vancitrix™ being generally regarded as safe when manufactured according to GMP.

## References

1. GRAS notification for BIOSECURE<sup>®</sup>, a hydro-glycerin citrus extract
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4. JPT Analytical Associates LLC, Gainesville, FL. Report: Detection, Identification and Quantification of Compounds
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7. J.A. Manthey and B.S. Buslig, "Distribution of Furanocoumarin in Grapefruit Juice Fractions", *J. Agric Food Chem.*, **2005**, 53, 5158-5163
8. ABC Research Laboratories, Gainesville, FL. Report: Minimum Inhibitory Concentration (MIC) of Organic GSE products against Four Selected Microorganisms.
9. <http://en.wikipedia.org/wiki/grapefruit>
10. 21 CFR 182.20
11. [www.fda.gov](http://www.fda.gov)

SUBMISSION END