ORIGINAL SUBMISSION

AIBMR
Life Sciences, Inc.

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Division of
Biotechnology and
GRAS Notice Review

Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety-CFSAN
U.S. Food and Drug Administration
5100 Paint Branch Parkway (HFS-200)
College Park, MD 20740-3835

May 30, 2013

ATTN: Moriama J. Ramos Valle

Our Reference: Updated (v.2) GRAS Notification for BIOSECUR®, a hydro-glycerin citrus extract

Dear Moriama,

As per our conversation, we are submitting an updated version of this GRAS notification prior to its official filing by FDA. We have made the following minor modifications to the Notification based on the pre-filing review:

1. We have modified the wording of the GRAS Exemption Claim.
2. We have modified the categories of food to exclude infant formula.
3. We have modified the Estimated Daily Intake section so as not to imply addition to categories of food that are regulated by USDA, and by providing additional reasoning/explanation behind the overall EDI calculation.

As mentioned in our last cover letter, AIBMR Life Sciences, Inc. has been retained as an agent by BIOSECUR Lab, Inc. ("the Notifier") to submit a GRAS notification to the FDA for BIOSECUR®, a hydroglycerin extract of *Citrus aurantium amara*, *Citrus reticulate*, and *Citrus sinensis*, intended for use as an ingredient in food. BIOSECUR® is therefore exempt from the requirement of pre-market approval, consistent with section 201 (s) of the Federal Food, Drug and Cosmetic Act.

The GRAS determination has been made based on scientific procedures. The basis for the determination relies on the FDA GRAS status and worldwide consumption profiles of the three citrus fruits from which the BIOSECUR® hydro-glycerin extract is manufactured, as compared to the very low estimated exposure levels of the ingredient. The hydro-glycerin extraction process does not lead to chemical alteration, and batch analyses show that the ingredient is made consistently and meets all specifications.

Please find enclosed a single copy and an electronic version of the updated notification: *Notice to US Food and Drug Administration that the use of BIOSECUR®, a Hydro-glycerin Citrus Extract, is Generally Recognized as Safe.* Also enclosed are copies of all references cited in the notification. As stated in the exemption claim, 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 BIOSECUR Lab, Inc., or will be sent to FDA upon request. Please do not hesitate to contact us with any questions.

Yours sincerely,

(b) (6)

John R. Endres
Chief Scientific Officer

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Chief Scientific Officer

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Notice to US Food and Drug Administration that the use of BIOSECUR®, a Hydro-glycerin Citrus Extract, is Generally Recognized As Safe

Submitted by the Notifier:

BIOSECUR Lab, Inc.

Prepared by the Agent of the Notifier:

AIBMR Life Sciences, Inc.
4117 S Meridian
Puyallup WA 98373

30 May 2013

Table of Contents

GRAS Exemption Claim 3
Name and Address of the Notifier 3
Common or Usual Name 3
Conditions of Use 3
Basis for GRAS Determination 3
Data/Information Availability Statement 3
Characterization 4
Chemical Composition 5
Organic Certification 5
Manufacturing and Production 6
Company Overview 6
Raw Materials 6
Manufacturing 6
Specifications and Batch Analysis 8
Specifications and Quality Control 8
Flavonoids 9
Microbial Assay 9
Heavy Metal Analysis 10
Essential Oil Components 10
Bitter Orange Synephrine 11
Citrus Limonoids 12
Product Homogeneity of Five Batches 12
Additional Analysis 14
Shelf-Life Stability 14
Self-limiting Levels of Use 14
Safety Assessment 15
Toxicological Studies 15
Investigation of Drug Interactions 15
Adverse Event Reports 16
History of Consumption 17
Current Regulatory Status 18
Regulatory Status of Citrus Fruits 18
Regulatory Status of BIOSECUR® Components 18
Information that may appear to be Inconsistent with GRAS Determination 19
Intended Use and Estimated Daily Intake (EDI) 19
General Recognition 21
Basis for the GRAS Determination 22
References 22

GRAS Exemption Claim

BIOSECUR Lab, Inc. (the notifier) has determined that BIOSECUR® 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 scientific procedures, and therefore the use of BIOSECUR®, for its intended purpose is exempt from the requirement of pre-market approval.

(b) (6)

05/30/2013

Yves Methot, Date

President, BIOSECUR Lab, Inc.

Name and Address of the Notifier

Yves Methot
BIOSECUR Lab, Inc.
P.O. Box 85123
Mont St-Hilaire, Quebec J3H 5W1
Canada

Common or Usual Name

BIOSECUR® is an organic hydro-glycerin extract from the following organic citrus fruits: *Citrus aurantium amara*, *Citrus reticulata*, and *Citrus sinensis*.

Conditions of Use

BIOSECUR® is intended for use as an ingredient at a concentration of up to 1500 ppm/serving 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 United States Department of Agriculture (USDA).

Basis for GRAS Determination

Scientific procedures are the basis for this GRAS determination.

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 BIOSECUR Lab, Inc., P.O. Box 85123, Mont St-Hilaire, Quebec J3H 5W1, Canada, or will be sent to FDA upon request.

Characterization

BIOSECUR® is BIOSECUR Lab's certified organic proprietary hydro-glycerin citrus extract, which is prepared from organic citrus fruits grown and harvested in Brazil. Three GRAS citrus species are used in the manufacturing of BIOSECUR® and include *Citrus aurantium amara*, *Citrus reticulata* and *Citrus sinensis*. *C. aurantium amara* is commonly known as bitter orange, sour orange, Seville orange or marmalade orange, and it is the citrus variety most commonly used in the preparation of marmalade fruit preserves (Masten 2004). The common name for *C. reticulata* is mandarin orange, and *C. sinensis* is commonly referred to as sweet orange or navel orange (Manner et al. 2006). Mandarin and navel oranges are found as fresh fruits and juices in grocery stores all over the globe. Due to its bitter nature, bitter oranges are not usually consumed as a fresh fruit, but are rather found as a fruit preserve or in other food commodities or juices. All three species are common ingredients in various food categories ranging from jams/jellies to salad dressings and marinades, among many other common condiments.

All three citrus species are also mentioned within the standards of identity for orange juice in the Code of Federal Regulations. 21 CFR 146.135 defines orange juice to contain unfermented mature *C. sinensis* or a hybrid orange called Ambersweet (a *C. sinensis* (1/2), *C. reticulata* (3/8) and *C. paradise* (1/8) hybrid). 21 CFR 146.140 states pasteurized orange juice content to be as specified in 21 CFR 146.135, and mentions further that *C. reticulata* or *C. reticulata* hybrids can be added, but at no more that 10%. According to 21 CFR 146.146, frozen concentrated orange juice is prepared by removing water from the juice as described in 146.135, to which may be added unfermented juice from mature oranges of the species *C. reticulata* (or hybrids), *C. aurantium,* or both. The volume of juice from *C. reticulata* (or hybrids) is not to exceed 10% in frozen concentrated orange juice, while the volume of juice from *C. aurantium* is not to exceed 5% of the unconcentrated (single strength) blend.

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). The United States is the second largest citrus fruit producer in the world, with over $20 billion in retail sales (Patil et al. 2006). A variety of citrus species are sold and consumed throughout the United States, and the 2000–2001 USDA Fact Book listed the annual per capita citrus fruit consumption to be 23.4 pounds (USDA 2002).

As will be discussed below, BIOSECUR® consists of common citrus polyphenols, including bioflavonoids, along with other natural occurring compounds and citrus biomass (Kawaii et al. 1999). BIOSECUR® is prepared from a combination of the three citrus fruits mentioned above, and the ratio of harvested citrus mixtures may vary based on seasonal availability. The citrus fruits are harvested

punctually during the months of July–August and February–March, and the product's batch-to-batch homogeneity is based on the total polyphenol content of resulting citrus mixtures.

No citrus peel is used in the manufacturing of BIOSECUR®. As will be described in the manufacturing process, fruits are washed and peeled before being processed. The peeled fruit (the edible part of the citrus), including the albedo component, is processed. All raw ingredients (glycerin, fruits, and organic acids) used to manufacture BIOSECUR® are food grade and FDA GRAS, and the citrus fruits and glycerin used are further certified organic. The glycerin is free of diethyl glycol (DEG), and no genetically modified organisms (GMOs)/ingredients are used in the manufacturing of BIOSECUR®. Rigorous physical and chemical characterization has been conducted on multiple batches of BIOSECUR® to thoroughly identify the product's chemical composition.

Chemical Composition

Certified Organic BIOSECUR® is a water-soluble and alcohol-free proprietary hydro-glycerin citrus extract prepared from organic citrus fruits. The article is a nonvolatile honey-colored clear/transparent liquid with a density of 1.11–1.22 g/mL, and a pH ranging from 2.0–3.5. It has a light citrus odor and its taste is slightly acidic, sweet and astringent (Table 1). BIOSECUR® contains approximately 4,765 μg of vitamin C (ascorbic acid)/100 g and is further comprised of approximately 60% glycerin, ~5% protein, and 2.70–5.00% total polyphenols. As will be discussed below, BIOSECUR® is synephrine-free and does not contain any citrus essential oils, limonin or nomilin.

Organic Certification

BIOSECUR® is Certified Organic by the National Organic Program (NOP) of the USDA and ECOCERT. Furthermore, BIOSECUR® manufacturing and marketing is compliant with the organic standards set forth by the Quebec Organic Reference Standards (CARTV) and the Canadian Organic Production Systems Standards (CAN/CGSB 32.310 and 32.311). BIOSECUR® is certified to the terms of the US-Canada Organic Equivalence Arrangement, and the manufacturing process of BIOSECUR® adheres to current Good Manufacturing Practices (GMP) standards. Ingredients used in the manufacturing of BIOSECUR® are not GMOs, nor are any ingredients used in the product from GMO origin. BIOSECUR® does not contain any carcinogenic, mutagenic or reprotoxic (CMR) substances—including dibutylphthalate (DBP), diethylhexylphthalate (DEHP) or butylbenzyl phthalate (BBP). Lastly, BIOSECUR® is manufactured using 99.5% pure Organic Certified glycerin. A Declaration for GED by the glycerin supplier, certifies the ingredient to be GED-free.

Manufacturing and Production

Company Overview

Quebec-based BIOSECUR LAB, Inc. develops non-toxic, Certified Organic, and environmentally safe plant-based bio-ingredients.

Raw Materials

The three organic citrus fruit species used in the production of BIOSECUR® (*C. aurantium amara, C. reticulata,* and *C. sinensis)* are grown and harvested by Certified Organic farmers in Brazil. Additional raw ingredients include water, organic and DEG-free vegetable glycerin (CAS# 56-81-5), lactic acid (CAS# 79-33-4), citric acid (CAS# 77-92-9) and ascorbic acid (CAS# 50-81-7). All ingredients used in the manufacturing of BIOSECUR® are FDA GRAS and used in most food categories in the United States.

Manufacturing

BIOSECUR Lab uses a variable mixture of three organic citrus fruits (*C. aurantium amara, C. reticulata,* and *C. sinensis)* of varying degrees/stages of maturity in the manufacturing of BIOSECUR®, the end product of which must meet total polyphenol specifications (2.70–5.00%) to ensure product homogeneity. Figure 1 outlines the manufacturing process of BIOSECUR®. As mentioned previously, the fruits are washed and peeled before entering the production phase. The resulting edible parts, including the albedo component, are extracted with water and glycerin by macerating the mixture. The pH of the mixture is adjusted to meet quality control standards and this is followed by a separation step to remove citrus solids. The resulting mixture is further concentrated and centrifuged. The supernatant (extract) is then quarantined prior to quality assessments, which include total citrus polyphenols, ascorbic acid content, and acidity (pH). Additional raw materials (ascorbic acid, lactic acid and citric acid) are added to the resulting extract, and this liquid is quarantined again to pass a second and final quality inspection that includes physical and chemical analysis, and organoleptic analyses. Upon approval, the product is ready for packaging.

FLOW CHART

BIOSECUR® – Citrus Extract

1- Selection of CERTIFIED ORGANIC citrus fruits
2- Fruits cleaning process
3- Equipment cleaning (organic procedure)
4- Weighing and measuring ingredients
5-First step production (addition of water and organic glycerin)
6-Active ingredients extraction by a hydro/glycerin maceration process
7- Pressed/filtered for solids separation
8- Mix and concentrate
9- Quality control stage / quarantine (Citrus polyphenols, Ascorbic acid, Acidity / pH)
10- Second step production (centrifuge)
11- Quality control stage
12- Third step production (add Citric acid, Lactic acid and Ascorbic acid)
13- Mix
14- Quality control stage
15- Bulk packaging
16- Quarantine stage
17- Quality control approval
18- Equipment cleaning (organic procedure)
19- Weighing ingredients
20- Fourth step production (to balance BIOSECUR formulation)
21- Add ingredients if necessary (Citric acid, Lactic acid and Ascorbic acid) and mix
22- In process analysis and approval for packing
23- Final Quality Control / Physic-Chemical and organoleptic analyses
24- Tracing / 3 samples per batch are stored for 3 years
25- Metal detection
26- Packing
27- Equipment cleaning (organic procedure)
28- Finished product analysis
29- Finished product release
30- Storage and distribution

Figure 1: Manufacturing Process Flow Diagram for BIOSECUR®

Specifications and Batch Analysis

Specifications and Quality Control

Production consistency of BIOSECUR® batches is accomplished through several rigorous analytical assays. As indicated in Table 1, three batches of BIOSECUR® were tested and show reasonable content consistency, meeting all specifications. Detailed descriptions of each component are provided hereafter along with analyses for essential oils, synephrine, citrus limonin and nomilin, and paraben. The citrus fruit mixture used in the preparation of batch 103/9 was harvested in August 2009, and the citrus fruit mixtures used in the preparation of batches 106/10 and 107/10 were harvested in February 2010.

Table 1: BIOSECUR® General Specifications and Chemical Characterization

Parameter	Specification	Method	Batch Number		
			103/09	106/10	107/10
Quality Control					
Liquid Appearance	Viscous crystalline honey color, light citrus odor	Organoleptic procedure	PASS	PASS	PASS
Water solubility	100%	USP XXII (1990)	PASS	PASS	PASS
Density (g/mL)	1.1900–1.2200	Brazilian Pharmacopeia, 1997	1.2030	1.2021	1.2042
pH 25°C (10% Sol)	2.00–3.50	USP XXII (1990)	2.53	2.47	2.51
Acidity (mg)*	1000–1300	Brazilian Pharmacopeia, 1997	1,085	1,101	1,096
Ascorbic Acid (%)	4 % Min.	AOAC 967.21	PASS	PASS	PASS
Refraction rate	1.47 (± 2%)	Via hand-held refractometer	PASS	PASS	PASS
Total Bioflavonoids	0.50–1.20%	Spectrophotometric analysis by Folin-Ciocalteu Method (GAE)	PASS	PASS	PASS
Total Polyphenols	2.7–5.00%	Spectrophotometric analysis by Folin-Ciocalteu Method (GAE)	PASS	PASS	PASS
General Composition					
Glycerin (%)	57–64%	GC-FID	60.1	58.4	60.5
Total Protein (%)	Not Applicable	AOAC 992.15, 991.43 and AACC 46–30 (modified)	5.34	5.05	5.54
Total Fiber (%)	0%	AOAC: 991.43 (Modified, MegaZyme Kit)	0	0	0
Water (%)	Not Applicable	DEV-10-028 99.1-CDXA-3.0000094 (Karl Fisher Assay)	8.5	7.78	7.5
Ascorbic Acid (%)	1.75–4%	HPLC	2.01	1.95	2.32
Citric Acid (%)	< 2%	HPLC	0.597	0.521	0.646
Lactic Acid (%)	< 2%	HPLC	NA	NA	1.49%

GAE, gallic acid equivalence method; BRL, detected below the reporting limit (the reporting limit for tangeritin is 0.049 mg/mL); NA, not analyzed; HPLC/UV-Vis, High Performance Liquid Chromatography (HPLC), USP; United States Pharmacopeia, AOAC; Association of Analytical Chemists, AACC; American Association of Cereal Chemists. *Quantity of product neutralized by 1 mL of 0.1 M NaOH.

Flavonoids

Three batches of BIOSECUR® (batches 103/9, 106/10 and 107/10) were examined for the presence of four flavonoids by ChromaDex™ (Irvine, CA): rutin, hesperidin, tangeritin and quercetin. High Performance Liquid Chromatography (HPLC) was employed in the assays and results verified the presence of all except tangeritin, which was below the reporting limit, as shown in Table 2.

Table 2: Polyphenol Content and Select Bioflavonoids

Polyphenol Content					
Analyte	**Specifications**	**Methods**	**Batch Number**		
			103/09	**106/10**	**107/10**
Total Polyphenol (%)	2.7–5.00%	Folin-Ciocalteu Method	4.32	3.86	3.85
Rutin (mg/mL)	NA	HPLC/ UV-Vis	3.92	2.27	3.99
Hesperidin (mg/mL)	NA	HPLC/ UV-Vis	0.00762	0.00534	0.00884
Quercetin (mg/mL)	NA	HPLC/ UV-Vis	4.38	2.70	4.49
Tangeritin (mg/mL)	NA	HPLC/ UV-Vis	BRL	BRL	BRL

High Performance Liquid Chromatography (HPLC) with Ultraviolet-Visible (UV-Vis) detector. Below Reporting Limit (BRL). Not applicable (NA).

Microbial Assay

Microbiological testing is performed on every batch of BIOSECUR® according to USP method 61. The tests are conducted to ensure that each batch of BIOSECUR® meets microbial limit specifications. Three batches (104/9, 106/10 and 107/10) are shown in Table 3. All batches met the specifications (<10 CFU/g) for yeast, mold and aerobic bacteria. Furthermore, all three batches met the specifications for no detection (ND) of *Escherichia coli (E. coli)*, *Pseudomonas aeruginosa, Salmonella sp.*, and *Staphylococcus aureus.*

Table 3. BIOSECUR® Microbial Analysis

Test	**Specifications**	**Method**	**Batch Number**		
			104/09	**106/10**	**107/10**
Total aerobic bacteria (CFU/g)	< 10	USP 61	< 10	< 10	< 10
Total yeast (CFU/g)	< 10	USP 61	< 10	< 10	< 10
Total mold (CFU/g)	< 10	USP 61	< 10	< 10	< 10
E.coli (CFU/g)	ND	USP 62	ND	ND	ND
Salmonella sp. (CFU/g)	ND	USP 62	ND	ND	ND
Staphylococcus aureus (CFU/g)	ND	USP 62	ND	ND	ND
Pseudomonas aeruginosa (CFU/g)	ND	USP 62	ND	ND	ND

ND, not detected above reporting limit.

Heavy Metal Analysis

BIOSECUR® batches 103/09, 106/10 and 107/10 were tested using an ICP-MS protocol to determine the presence of the following heavy metals: lead, arsenic, cadmium, and mercury, as shown in Table 4.

Table 4: Heavy Metals Analysis

Heavy Metal	Specifications	Reporting Limit (ppm)	Batch Number		
			103/09	106/10	107/10
Arsenic (ppm)	ND	0.5	ND	ND	ND
Cadmium (ppm)	ND	0.5	ND	ND	ND
Lead (ppm)	ND	0.5	ND	ND	ND
Mercury (ppm)	ND	0.5	ND	ND	ND

ND: not detected above reporting limit.

BIOSECUR® batch number 107/10 was subjected to additional heavy metal testing by Eurofins testing laboratory using ICP-MS. This analysis confirms that the heavy metals tested for in BIOSECUR®, as shown in Table 5 were below the level of detection.

Table 5. Additional Heavy Metal Analysis for BIOSECUR® Batch 107/10

Heavy Metal	Specifications	Reporting Limit (mg/mL)	Content
Arsenic	< 0.02 mg/kg	0.02 mg/kg	< 0.02 mg/kg
Cadmium	< 0.01 mg/kg	0.01 mg/kg	< 0.01 mg/kg
Lead	< 0.02 mg/kg	0.02 mg/kg	< 0.02 mg/kg
Mercury	< 0.01 mg/kg	0.01 mg/kg	< 0.01 mg/kg

Essential Oil Components

As previously mentioned, BIOSECUR® does not contain any citrus peel or citrus peel components—the parts of the fruit that contain the majority of essential oils. Fruits are washed and peeled before being processed and only the edible parts of the citrus, including the albedo component, are used. Essential Oil analysis of 3 batches of BIOSECUR® (batch 103/09, 106/10, and 107/10) were conducted using Gas Chromatography-Mass Spectrometry (GC-MS) by ChromaDex™ to test for the presence of an array of essential oils. No essential oils tested for were detected above reporting limits, as shown in Table 6.

Table 6. Essential Oil Analysis

Essential Oil	Reporting Limit (ppm)	Batch Number		
		103/09	106/10	107/10
Limonene	17	BRL	BRL	BRL
Linalool	17	ND	ND	ND
Benzyl alcohol (ppm)	19	BRL	BRL	BRL
DL-b-Citronellol	16	ND	ND	ND
Estragole	17	ND	ND	ND
Methyl-2-octynoate	17	ND	ND	ND
Geraniol	17	ND	ND	ND
Citral (A)	7	ND	ND	ND
Citral (B)	11	ND	ND	ND
Hydroxycitronellal	19	ND	ND	ND
Methyl-2-nonynoate	19	ND	ND	ND
t-Cinnamaldehyde	17	ND	ND	ND
Anisyl Alcohol (4-mthoxy-Benzyl Alcohol)	16	ND	ND	ND
Cinnamyl Alcohol	17	ND	ND	ND
Eugenol	16	ND	ND	ND
Eugenol methyl ether	17	ND	ND	ND
Isoeugenol	17	ND	ND	ND
BMHCA	17	ND	ND	ND
Coumarin	15	ND	ND	ND
Amylcinnamaldehyde	17	ND	ND	ND
Farnesol	8	ND	ND	ND
HMPCC	11	ND	ND	ND
Hexylcinnamaldehyde	17	ND	ND	ND
Benzyl benzoate (ppm)	20	BRL	BRL	BRL
Benzyl Salicylate	21	ND	ND	ND
Benzyl Cinnamate	18	ND	ND	ND

BRL: Below reporting limit. ND: not detected

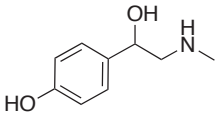
Bitter Orange Synephrine

It is well known that *C. aurantium amara* contains *para*-synephrine, which is a compound with structural and chemical similarities to ephedrine—an α-adrenergic agonist (Pellati et al. 2002; Jordan et al. 2004; Pellati et al. 2004; Pellati et al. 2007). Ephedrine was previously sold as a weight loss dietary ingredient in the United States before being banned by FDA in 2004 (Thompson 2004). While it is often assumed that synephrine will behave similarly in the body to ephedrine, and thus may have the potential for adverse effects when consumed, small structural differences between the two molecules result in different receptor-binding profiles (Stohs et al. 2011).

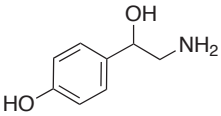
The *R*-(–)-enantiomer of *para*-synephrine (also referred to as the *l*-form or natural form) is the isomer found in *C. aurantium amara* (Stohs et al. 2012). The majority of the *para*-synephrine in methanol extracts of unripe *C. aurantium amara* was found in the citrus peel: consisting of 0.056% of the peel, 0.028% of the albedo and 0.019% of the pulp when analyzed using HPLC with diode array detector (HPLC-DAD) (Arbo et al. 2008). Another author reported the *para*-synephrine content of unripe *C. aurantium* to be 2.52 mg/g dry weight (which amounts to 0.0252%) (Pellati et al. 2007). An aqueous extract of fresh fruit pulp had a *para*-

synephrine content of 0.02% by HPLC-DAD and this value was 0.352% for an extract prepared from pulverized commercial dried fruit (Pellati et al. 2002). Fresh fruit dried at 50 ºC in a forced-air oven had a *para*-synephrine content of 0.10% dry weight by reverse phase (RP) HPLC-DAD; this value was 0.35% for commercial dried fruit (Pellati et al. 2004). Additionally, mature peel was reported to have a 0.75 mg/g dry weight *para*-synephrine content by HPLC (Pellati et al. 2007).

An independent laboratory was contracted to determine the presence of synephrine and other adrenergic amines in BIOSECUR® using HPLC/UV-Vis. In addition to synephrine, *C. aurantium* has also been found to contain the adrenergic agonists octopamine and hordenine (Putzbach et al. 2007). As such, these two compounds were also included in the analysis. ChromaDex™ (Irvine, CA) performed the analysis.



para-Synephrine



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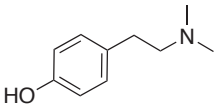

Hordenine

Bitter orange adrenergic amine analysis was conducted on 3 batches of BIOSECUR® (batches 103/09, 106/10, and 107/10). As shown in Table 7, none of the hydroxyphenyl amines in question were detected above the assay's detectable limits.

Table 7. Bitter Orange Adrenergic Amine Analysis

Adrenergic Amine	Reporting Limit (Limit of Detection)	Batch Number		
		103/09	106/10	107/10
Synephrine (%)	0.004	ND	ND	ND
Octopamine (%)	0.005	ND	ND	ND
Hordenine (%)	0.005	ND	ND	ND

ND, not detected above reporting limit.

Citrus Limonoids

Citrus limonoid analysis was conducted on 3 batches of BIOSECUR® (batches 103/09, 106/10, and 107/10) using HPLC, to determine the presence of limonin and nomilin. These two limonoids were first identified as bitter components of citrus seeds (Patil et al. 2009). Neither of the two limonoids was detected above the assay's limit of detection.

Product Homogeneity of Five Batches

Five different batches of BIOSECUR® (batches 102/09,103/09, 104/09, 106/10, and 107/10) were assessed to establish overall product homogeneity. For this identity analysis, Thin Layer Chromatography (TLC) was employed using Silica gel 50, F245 HP-TLC plates and an ethyl acetate/acetic acid/formic acid/Milli-Q

water (10/1.1/1.1/2.6) mobile phase. TLC is a classical and reliable method used in the analysis of botanical extracts and the TLC fingerprint provides qualitative analysis of plant extract constituents (Ramirez-Duron et al. 2007). It is used in establishing extract and product homogeneity, and is an important tool used in quality control.

ChromaDex™ (Irvine, CA) conducted this botanical identity testing analysis. Samples from the five batches were analyzed (developed) side-by-side to compare their chemical profiles and thus verify the product homogeneity. The analysis was conducted at two concentrations, 3 and 6 μL, and the retardation factors (Rf values) of the resulting TLC spots were recorded. The TLC spots were visualized using various TLC visualization solutions: UV light wavelengths (254 nm and 365 nm), illuminated with white light and vanillin/sulfuric acid visualization spray. All five samples resulted in almost identical Rf profiles—a strong indication of production homogeneity for batches prepared from various mixtures/ratios of the three citrus species, as shown in Table 8.

Table 8. TLC Botanical Identity Testing Results

TLC Results (Rf values and spot colors)						
Visualized	**UV light 254 nm**	**UV light 365 nm**	**White light & vanillin/sulfuric acid staining**	**UV light 254 nm**	**UV light 365 nm**	**White light & vanillin/sulfuric acid staining**
Batch Number	**3 μl Applied**			**6 μl Applied**		
103/09	0.27 (blue) 0.34 0.39 0.43 (blue) 0.47 0.90	0.08 0.28 0.37 0.43 0.89 (tan)	0.12 (purple) 0.18 (purple) 0.27 (purple) 0.35 (tan) 0.39 (tan) 0.43 (tan) 0.48 (purple) 0.53 (purple) 0.91 (tan)	0.27 (blue) 0.34 0.39 0.43 (blue) 0.47 0.90	0.08 0.28 0.37 0.43 0.89 (tan)	0.12 (purple) 0.18 (purple) 0.27 (purple) 0.35 (tan) 0.39 (tan) 0.43 (tan) 0.48 (purple) 0.53 (purple) 0.91 (tan)
104/09	0.27 (blue) 0.33 0.38 0.42 (blue) 0.47 0.89	0.08 0.28 0.36 0.42 0.89 (tan)	0.11 (purple) 0.18 (purple) 0.28 (purple) 0.34 (tan) 0.38 (tan) 0.43 (tan) 0.47 (purple) 0.52 (purple) 0.90 (tan)	0.27 (blue) 0.33 0.38 0.42 (blue) 0.47 0.89	0.08 0.28 0.36 0.42 0.89 (tan)	0.11 (purple) 0.18 (purple) 0.28 (purple) 0.34 (tan) 0.38 (tan) 0.43 (tan) 0.47 (purple) 0.52 (purple) 0.90 (tan)
106/10	0.27 (blue) 0.33 0.38 0.42 (blue) 0.46 0.89	0.08 0.28 0.36 0.42 0.88 (tan)	0.11 (purple) 0.17 (purple) 0.28 (purple) 0.33 (tan) 0.38 (tan) 0.42 (tan) 0.46 (purple) 0.51 (purple) 0.90 (tan)	0.27 (blue) 0.33 0.38 0.42 (blue) 0.46 0.89	0.08 0.28 0.36 0.42 0.88 (tan)	0.11 (purple) 0.17 (purple) 0.28 (purple) 0.33 (tan) 0.38 (tan) 0.42 (tan) 0.46 (purple) 0.51 (purple) 0.90 (tan)
107/10	0.27 (blue) 0.33 0.38 0.42 (blue) 0.47 0.89	0.08 0.28 0.36 0.41 0.88 (tan)	0.10 (purple) 0.17 (purple) 0.27 (purple) 0.33 (tan) 0.38 (tan) 0.42 (tan) 0.46 (purple) 0.51 (purple) 0.90 (tan)	0.27 (blue) 0.33 0.38 0.42 (blue) 0.47 0.89	0.08 0.28 0.36 0.41 0.88 (tan)	0.10 (purple) 0.17 (purple) 0.27 (purple) 0.33 (tan) 0.38 (tan) 0.42 (tan) 0.46 (purple) 0.51 (purple) 0.90 (tan)
102/09	0.27 (blue) 0.33	0.08 0.27	0.11 (purple) 0.18 (purple)	0.27 (blue) 0.33	0.08 0.27	0.11 (purple) 0.18 (purple)

	0.37 0.42 (blue) 0.47 0.89	0.36 0.43 0.89 (tan)	0.28 (purple) 0.33 (tan) 0.39 (tan) 0.43 (tan) 0.47 (purple) 0.52 (purple) 0.90 (tan)	0.37 0.42 (blue) 0.47 0.89	0.36 0.43 0.89 (tan)	0.28 (purple) 0.33 (tan) 0.39 (tan) 0.43 (tan) 0.47 (purple) 0.52 (purple) 0.90 (tan)

Additional Analysis

BIOSECUR® batch number 107/10 was subjected to a pesticide screen (Luke II Multiresidue Screen), performed by Eurofins (Petaluma, CA), to detect the presence of the following groups of pesticides: carbamates, organophosphates, organonitrogens, organochlorines, and pyrethroids. No pesticides were found at levels above the detectable limit in the product. Additional pesticide screening was conducted on three batches (103/09, 106/10 and 107/10) of BIOSECUR® (performed by ChromaDex™) and none of the analytes tested were detected. As mentioned previously, the three organic citrus fruit species used in the manufacturing of BIOSECUR® are grown and harvested by Certified Organic farmers located in Brazil, South America. As such, pesticide testing of every batch is not deemed necessary.

BIOSECUR® batch number 104/09 was tested by TransBioTech for the presence of parabens—a class of common preservatives used as food additives. Analysis with Ultra Performance Liquid Chromatography Tandem Mass Spectrometry (UPLC-MS-MS) determined the product to be paraben-free (analysis was for methyl, ethyl, propyl, isopropyl, butyl and isobutyl paraben).

BIOSECUR® batch number 104/09 was tested for the presence of food preservatives (benzalkonium chloride, benzethonium chloride and triclosan) using HPLC-UV-MS analysis. The analysis confirmed the absence of these classes of food preservatives in the product.

Shelf-Life Stability

BIOSECUR® batch number 103/10 was subjected to an accelerated shelf-life stability test for a period of three months at 50° C ± 2° C and 90% relative humidity. The batch was tested monthly, and after three months of accelerated degradation conditions the product still met all of the original specifications that were assayed: appearance and organoleptic characteristics, water solubility, pH, ascorbic acid content, total bioflavonoid content and total polyphenol content.

Self-limiting Levels of Use

When added to food as an ingredient at levels greater than 500 ppm, a taste associated with BIOSECUR® is detected and is likely to self-limit its use above this concentration; however in some food applications levels up to 1500 ppm may be used.

Safety Assessment

Toxicological Studies

Historically, there have been no safety concerns associated with the consumption of *C. reticulata* and *C. sinensis*, and as such, safety assessments are absent from the public domain despite widespread consumption of fruit from these species. Studies have been performed on the safety of citrus peel from various species, but these are not relevant since the peels of the citrus fruits are removed prior to manufacturing BIOSECUR®.

A large collection of safety studies on *C. aurantium amara* extracts is available in the public domain. These studies focus on extracts specifically standardized to synephrine content. As previously stated, various batches of BIOSECUR® have been tested and neither synephrine, nor octopamine nor hordenine have been detected (Table 7). Because of this, the studies are not considered relevant and are not included herein.

Investigation of Drug Interactions

Grapefruit juice has been studied extensively with regard to its effects on the bioavailability of drugs, and is known to affect drug metabolism in the intestines, via CYP3A enzymes and p-glycoprotein transporters. The effect can occur even if the juice is not taken simultaneously with the medication (Rodriguez-Fragoso et al. 2011). Seville (bitter) orange juice has also been shown to affect drug bioavailability (Hou et al. 2000; Di Marco et al. 2002; Penzak et al. 2002). Common sweet orange juices don't appear to have the same effect (Malhotra et al. 2001; Penzak et al. 2002; Rodriguez-Fragoso et al. 2011). Consumption of orange juice and vitamin C are also well known to aid in the absorption of iron from the gastrointestinal tract (Balay et al. 2010).

It is important to point out that potential drug interactions are suspected for many common fruits and vegetables that humans consume on a daily basis (Rodriguez-Fragoso et al. 2011). For example, both orange and apple juice (200 mL) were shown to reduce the plasma concentrations of the antihypertensive drug aliskiren (Tapaninen et al. 2011). In vitro and/or animal studies suggest that the following fruits and vegetables may interact with drug-metabolizing enzymes, transport proteins, or may have other types of food-drug interactions: tangerines, grapes, cranberries, pomegranates, mangos, guava, raspberries, apples, broccoli, watercress, tomatoes, avocados, asparagus, cauliflower, celery, eggplant, parsley, onions, and more (Rodriguez-Fragoso et al. 2011). These are the same fruits and vegetables recommended by the World Health Organization (WHO) and the Agricultural Organization of the United Nations (FAO) as necessary to maintain an optimum nutrient intake for good human health. Additional studies in humans are needed to further understand these types of interactions.

Both grapefruit juice (1:3 of 100% pure frozen concentrate to water) and Seville orange juice (200 mL of fresh squeezed) were found to increase the bioavailability of the anti-tussive agent dextromethorphan (DM) in a small pharmacokinetic study consisting of 11 subjects (Di Marco et al. 2002). The

results were obtained using measurements of urine metabolites over 8 hours. Both juices appeared to affect CYP3A enzymes and/or P-glycoprotein transporters in the intestinal gut wall but not the CYP enzymes of the liver.

Furanocoumarins (including 6′7′-dihydroxybergamottin) in both grapefruit juice and Seville orange juice are thought to be involved in the inhibition of CYP3A4 in the gastrointestinal tract, although other compounds in the citrus fruits may be responsible for the effects on P-glycoprotein. Both of the compounds involved and the effects on this transporter are under study and may differ between grapefruit and bitter orange (Edwards et al. 1999; Malhotra et al. 2001; Rodriguez-Fragoso et al. 2011).

The 200 mL of juice used in many of the studies (for both grapefruit and bitter orange juice) is equivalent to approximately 0.85 cups, or 211 grams—of which approximately 186 grams are water (according to the USDA National Nutrient Database for Standard Reference, Release 25); hence, approximately 25 grams dry weight.

The flavonoid/polyphenolic content of orange juice has been measured in various papers and has been reported as ranging from approximately 35 mg/100 mL to over 60 mg/100 mL, using various methods of analysis (Rapisarda et al. 1999; Arabbi et al. 2004; Vanamala et al. 2006; Klimczak et al. 2007). Using this information, ingestion of 200 mL of juice may be equivalent to ingestion of 70–120 mg of polyphenols.

As will be discussed in detail in the Estimated Daily Intake (EDI) section, the maximum exposure level of BIOSECUR® under its intended conditions of use is 775 mg per day, of which 60% is glycerin; thus is equivalent to 310 mg of non-glycerin ingredients (including citrus extracts). In comparison, this is equivalent to a total polyphenol intake (from all three fruits—*C. aurantium*, *C. reticulata*, and *C. sinensis*) of up to 40 mg per day, based on the BIOSECUR® ingredient specifications for polyphenols. At this intended use level, exposure to the BIOSECUR® ingredient is not expected to lead to adverse drug interactions.

Adverse Event Reports

Several publications and case reports on weight loss supplements containing *C. aurantium* extracts have reported adverse events. These are isolated cases, many of the individuals had pre-existing conditions, and the supplements taken generally contained multiple ingredients; therefore, it is impossible to determine which ingredient or combination of ingredients might have been responsible for the effects. Most importantly, the ingredients in question contained synephrine, which has not been found in analytical testing of BIOSECUR®. Because of this, these case reports were deemed irrelevant and are not discussed herein.

Bitter oranges are considered a common human food commodity consumed worldwide, as is exemplified by the fact that the standard of identity for frozen concentrated orange juice includes optional juice from this fruit (21 CFR 146.146).

History of Consumption

The three citrus species used in the manufacturing of BIOSECUR® include *C. aurantium amara*, *C. reticulata* and *C. sinensis*. All three have a very long history of human use worldwide. As stated previously, the 2000–2001 United States Department of Agriculture (USDA) Fact Book listed the annual per capita United States citrus fruit consumption to be 23.4 pounds (USDA 2002). The juice and peel of *C. aurantium amara* are used in the preparation of marmalade fruit preserves, consumed around the globe. Due to its bitter taste, bitter oranges are mainly used as a fruit preserve and are popular in sorbet recipes. *C. reticulata* is sold in grocery stores as a fresh or canned fruit, and *C. sinensis* is also a popular citrus fruit found in grocery stores worldwide. The immature *C. sinensis* fruit is also used often in Indian cuisine, and is sometimes referred to as narthangai.

All three species are sold as juices, are used to prepare jellies or jams, and are common ingredients in various additional food sources such as salad dressings and marinades as shown in Table 10.

Table 10: Common Citrus Fruit Products

	Citrus aurantium amara (Bitter Orange, Seville and Marmalade Orange)	***Citrus reticulata*** (Mandarin Orange)	***Citrus sinensis*** (Sweet or Navel Orange)
Fresh Fruits		Satsuma Mandarins	Sunkist Fresh Fruits
Canned Fruits		Natural Value Mandarin Orange Sections Native Forest Organic Mandarin Oranges Dole Fruit Cups	
Juices	Fentimans Mandarin & Seville Orange Jigger (juice)	Dole Orange Juice Fentimans Mandarin & Seville Orange Jigger (juice)	Dole Orange Juice Sunkist
Jams and Jellies	Helios Seville Bitter Orange Fruit Preserve MACKAY'S Seville orange Marmalade	Aline Berry Farm Mandarin Jam Bonne Maman Manderin Preserve	Smuckers Sweet Orange Marmalade
Marinades	Goya Bitter Orange Marinade Conchita Bitter Orange Marinade La Lechonera Bitter Orange Marinade Naranja Agria Bitter Orange Marinade	Lawry's Marinade with Mandarin Juice Simply Asai Mandarin Orange Stir Fry Sauce	Chef LaLa Momemade Orange Chipolte Marinade
Salad Dressings		Briannas Saucy Ginger Mandarin Dressing	
Other		CaJohn's Gourmet Mandarin Salsa	Marie Sharps Sweet Orange Salsa

Current Regulatory Status

Regulatory Status of Citrus Fruits

The concentration of each citrus fruit used in the production of BIOSECUR® (*C. aurantium amara, C. reticulata* and *C. sinensis*) may vary slightly with seasonal availability. *C. reticulata* and *C. sinensis* fruits are FDA GRAS in accordance with 21 CFR 182.20, which lists these under "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." According to 21 CFR 146.146(a), *C. aurantium* and *C. reticulata* may be used in the preparation of concentrated orange juice at levels not to exceed 5% and 10% of the unconcentrated volumes, respectively. The relevant citrus components described in 21 CFR are listed in Table 11.

Table 11: GRAS Status of BIOSECUR® Fruits

Description or Common name	Botanical name	21 CFR Reference
C. sinensis or hybrids	*Citrus sinensis*	146.135
C. reticulata or hybrids	*Citrus reticulata*	146.135
C. aurantium	*Citrus aurantium*	146.146
C. reticulata or hybrids	*Citrus reticulata*	146.146
Mandarin	*Citrus reticulata Blanco.*	182.20
Tangerine	*Citrus reticulata Blanco.*	182.20
Orange, sweet	*Citrus sinensis (L.) Osbeck.*	182.20

BIOSECUR® F440D has also been approved by the Bureau of Chemical Safety, Health Canada, as a flavor additive for addition to non-standardized food products at 400–1500 ppm. Furthermore, all additional raw ingredients used during the manufacturing of the BIOSECUR® are considered FDA GRAS in accordance with the discussions below.

Regulatory Status of BIOSECUR® Components

- As listed in Table 11, all of the citrus fruits used to manufacture BIOSECUR® are FDA GRAS in accordance with 21 CFR 182.20, 21 CFR 146.135, and 21 CFR 146.146.
- Citric acid (CAS #77929) is considered FDA GRAS for use in foods with no limitations other than current good manufacturing practice, in accordance with 21 CFR 184.1033 and 21 CFR 184.1(b)(1).
- 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 considered FDA GRAS as a food ingredient in accordance with 21 CFR 184.1061 with no limitations other than current

good manufacturing practice. In accordance with 21 CFR 184.1061(c)(1), good manufacturing practice conditions include: "The ingredient is used as an antimicrobial agent as defined in 170.3(o)(2); a curing and pickling agent as defined in 170.3(o)(5); a flavor enhancer as defined in 170.3(o)(11); a flavoring agent and adjuvant as defined in 170.3(o)(12); a pH control agent as defined in 170.3(o)(23); and a solvent and vehicle as defined in 170.3(o)(27)." Lactic acid is GRAS as an ingredient in food with the exception of infant foods and formulas. Lactic acid is a raw ingredient that is used during manufacturing of BIOSECUR® as a pH control agent.

- 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.

Information that may appear to be Inconsistent with GRAS Determination

All three citrus species are GRAS and used in a wide range of consumed goods. There is nothing in the literature to suggest that any adverse events are associated with exposure to the water extracts or extract constituents of the citrus fruits in question. As discussed above, *para*-synephrine has been identified in the literature in *C. aurantium amara*. However, BIOSECUR® is free of citrus peel or peel extracts and batch analyses confirm that no synephrine or related adrenergic amines are present in BIOSECUR®.

Intended Use and Estimated Daily Intake (EDI)

BIOSECUR® 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 most frequently at a concentration of 500 ppm, with a maximum concentration of 1500 ppm. The estimated daily intake (EDI) or exposure to BIOSECUR® 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 BIOSECUR® by calculating 1500 ppm of total food intake (0.15%). 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 12 (EPA 2011). Data was collected from surveying 20,000 individuals on two non-consecutive days. If BIOSECUR® were added to all food categories listed in the

EPA report at 1500 ppm (0.15%) per day, then an individual aged ≥ 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 1.6 g of BIOSECUR® (1050 g x 0.15% = 1.6 g). This value would be approximately 3 g of BIOSECUR® for individuals in the 95th 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 0.15% = 2.9 g of BIOSECUR® per day). For children aged 3–6 years, exposure for the 95th percentile would also be approximately 3 g (102 g food/kg bw x 20 kg bw x 0.15%).

Table 12: Daily BIOSECUR® Exposure Based on EPA Data, if it were added to all foods consumed.

	Per Capita Total Food Intake from Major Food Groups (Edible and Uncooked) (g/kg bw)			Exposure to BIOSECUR® if added to all foods (addition level of 1500 ppm) Based on the Per Capita Total Food Intake from Major Food Groups (Edible and Uncooked)* (g/kg bw)		
Age group	Mean	10th %	95th %	Mean	10th %	95th %
3 to < 6	61	34	102	0.0915	0.051	0.153
6 to < 11	40	21	70	0.06	0.0315	0.105
11 to < 16	24	11	45	0.036	0.0165	0.0675
16 to < 21	18	8	35	0.027	0.012	0.0525
≥ 20	15	8	28	0.0225	0.012	0.042

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 BIOSECUR® likely to be consumed per day was calculated to be approximately 2.7–3.1 g based on consumption data for 1980–2009 (U.S. Census Bureau 2012). The majority of the food consumption data was calculated in the Census Bureau report 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 2.7–3.1 g of BIOSECUR® per day at a level of 1500 ppm or 0.015%.

Calculations using data from both the EPA Exposure Factors Handbook and the US Census Bureau 2012 Statistical Abstract resulted in a nearly identical exposure factor. Based on both calculations above, exposure to BIOSECUR® would be 1.6–3.1 g/day if the ingredient were added to all major food categories consumed throughout the day over a lifetime at the maximum concentration of 1500 ppm. For a number of reasons, a more reasonable exposure estimate would be that a maximum of 25% of a high-end user's diet would contain BIOSECUR® at its highest intended concentration, resulting in exposure to a maximum of approximately 775 mg of the ingredient per day. We believe that this leads to a more reasonable exposure estimate, for the following reasons: a) approximately 13% of the data from both the EPA Exposure Factors Handbook and the US

Census Bureau 2012 Statistical Abstract were based on USDA regulated categories of foods. However, BIOSECUR® is not intended to be added to USDA regulated categories of food under this GRAS notification; b) cost limitations and standards of identity will likely prohibit the addition of this ingredient to many foods; c) the average intended use of BIOSECUR® is at a significantly lower concentration (500 ppm), as compared to the maximum intended use of 1500 ppm which was used in the previous calculations.

Approximately 60% of BIOSECUR® is glycerin, thus approximately 465 mg of the exposure will be to glycerin, while exposure to the citrus and other non-glycerin components equate to a daily maximum of approximately 310 mg. According to BIOSECUR® specifications, exposure to 775 mg of the ingredient is equivalent to exposure of up to 40 mg total citrus polyphenols. In comparison, daily polyphenol intake levels from the diet have been estimated at approximately 1 g per day (Scalbert et al. 2000; Ovaskainen et al. 2008; Perez-Jimenez et al. 2011). Similarly, as referenced previously, a single glass of orange juice may contain over 120 mg of total citrus polyphenols. Hence the high-end exposure estimate would only constitute a fraction of the total polyphenol intake per day.

Similarly, the USDA National Nutrient Database lists the weight of fruit from one raw Florida orange at approximately 150 g, of which approximately 87% is water. Hence the dry weight of a single orange is approximately 19.5 g. It is common and not considered a safety concern to eat several oranges per day, equivalent to approximately 40 g if two pieces of fruit were consumed. This can be roughly compared to the much lower exposure of 310 mg of the non-glycerin component of BIOSECUR® per day. While raw oranges are not a perfect comparison for BIOSECUR®, because the latter is an extract, this example gives some additional perspective as to reasonable certainty of safety from consumption of this ingredient at the intended use level and resulting low level of exposure.

General Recognition

The information that provides the basis of this GRAS determination by scientific procedures is available in the public domain. The reference section of this notification cites all published studies, and citations to pertinent government regulations are listed throughout the dossier. All of the constituents used to prepare BIOSECUR® are recognized by FDA as GRAS, and there is currently no data that we are aware of that would argue against their current regulatory status. There is consensus that this ingredient, when manufactured according to GMP, is generally recognized as safe for its intended use as stated in this notification. Published scientific data, government positions that encourage the use of citrus fruits as food, as well as the broad availability of this ingredient in the marketplace, provide ample evidence of consensus among qualified experts that there is reasonable certainty that consumption of BIOSECUR® is safe under its conditions of intended use. The general availability of this information satisfies the common knowledge component of this GRAS notification.

Basis for the GRAS Determination

Based on an independent and collective critical evaluation of the available data and information described above, the notifier concludes that BIOSECUR Labs' organic hydro-glycerin citrus extract ingredient, BIOSECUR®, when produced in accordance with Good Manufacturing Practices, and meeting the specifications presented herein is generally recognized as safe for its intended use as a food ingredient based on scientific procedures, and is hence exempt from the requirement of premarket approval. Pivotal to this conclusion is the FDA GRAS status and worldwide consumption profiles of the three citrus fruits from which the BIOSECUR® hydro-glycerin extract is manufactured, as compared to the very low estimated exposure levels of the ingredient. The hydro-glycerin extraction process does not lead to chemical alteration, and batch analyses show that the ingredient is made consistently and meets all specifications.

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