LEMBAGA MINYAK SAWIT MALAYSIA
Malaysian Palm Oil Board
Kementerian Perusahaan Perladangan dan Komoditi
(Ministry of Plantation Industries and Commodities)

Ruj. Tuan I Your Ref.:

Ruj. Kami I Our Ref. :

24th May 2021

Dr. Paulette Gaynor
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740 USA

Dear Dr. Gaynor,

GRAS Notice for Water-Soluble Palm Fruit Extract

The above subject is kindly referred.

2. In accordance with 21 CFR §170 Subpart E consisting of § 170.203 through 170.285, the Malaysian Palm Oil Board (MPOB), as the notifier, is submitting one hard copy and one electronic copy (on CD), of all data and information supporting the conclusion that Water-Soluble Palm Fruit Extract, is GRAS on the basis of scientific procedures, for use In conventional food and beverage products across multiple categories. These food uses of Water-Soluble Palm Fruit Extract are therefore not subject to the premarket approval requirements of the *Federal* Food, *Drug and Cosmetic Act* Information setting forth the basis for MPOB's GRAS conclusion, as well as a consensus opinion of an independent panel of experts, also are enclosed for review by the agency.

3. I certify that the enclosed electronic files were scanned for viruses prior to submission and are thus certified as being virus-free using Symantec Endpoint Protection 12.1.5.

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

Thank you.

Your,; since L

DR. AHMAD PARVEEZ GHULAM KADIR
Director-General

GRAS NOTICE FOR WATER-SOLUBLE PALM FRUIT EXTRACT

SUBMITTED TO:
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition (CFSAN)
Food and Drug Administration
5001 Campus Drive
College Park, MD
20740 USA

SUBMITTED BY:
Malaysian Palm Oil Board
6, Persiaran Institusi
Bandar Baru Bangi
43000 Kajang
Selangor, Malaysia

DATE:
21 May 2021

GRAS Notice for Water-Soluble Palm Fruit Extract

TABLE OF CONTENTS

List of Appendices

List of Figures and Tables

GRAS Notice for Water-Soluble Palm Fruit Extract

Part 1. §170.225 Signed Statements and Certification

In accordance with 21 CFR §170 Subpart E consisting of §§170.203 through 170.285, the Malaysian Palm Oil Board (MPOB) hereby informs the United States (U.S.) Food and Drug Administration (FDA) that the intended uses of Water-Soluble Palm Fruit Extract (wsPFE) in various conventional food and beverage products, as described in Section 1.4 below, are not subject to the premarket approval requirements of the *Federal Food, Drug, and Cosmetic Act* based on the MPOB's view that these notified uses of wsPFE are Generally Recognized as Safe (GRAS). In addition, as a responsible official of the MPOB, the undersigned hereby certifies that all data and information presented in this notice represents a complete and balanced submission that is representative of the generally available literature. The MPOB considered all unfavorable as well as favorable information that is publicly available and/or known to the MPOB and that is pertinent to the evaluation of the safety and GRAS status of wsPFE as a food ingredient for addition to conventional food and beverage products, as described herein.

Signed,

21 May 2021

Ahmad Parveez Ghulam Kadir
Director-General
Malaysian Palm Oil Board
parveez@mpob.gov.my

Date

1.1 Name and Address of Notifier

Malaysian Palm Oil Board
6, Persiaran Institusi
Bandar Baru Bangi
43000 Kajang
Selangor, Malaysia

1.2 Common Name of Notified Substance

Water-Soluble Palm Fruit Extract (wsPFE); Palm Fruit Bioactive Complex (PFBc); Oil palm phenolics (OPP); Palm fruit juice (PFJ) phenolics

1.3 Trade Names

PFBc™

1.4 Conditions of Use

The wsPFE is intended for use as a food ingredient in a variety of conventional food and beverage products at levels ranging between 0.11% to 2.67%. The wsPFE is intended for use in sugar substitute products at levels up to 40%. A summary of the food categories and use levels in which wsPFE is intended for use is provided in Table 1.4-1 below. Food uses are organized according to 21 CFR §170.3 (U.S. FDA, 2020).

Table 1.4-1 Summary of the Individual Proposed Food Uses and Use Levels for Water-Soluble Palm Fruit Extracts in the U.S.

Food Category (21 CFR §170.3) (U.S. FDA, 2020)	Proposed Food Uses[a]	wsPFE Use Levels (g/serving), as consumed	RACC[b] (g or mL)	wsPFE Use Levels (g/100 g), as consumed
Baked Goods and Baking Mixes	Cookies	0.40	30	1.33
Beverages and Beverage Bases	Energy drinks	0.40	360	0.11
	Soft drinks	0.40	360	0.11
	Sport or electrolyte drinks, fluid replacement drinks[c]	0.40	360	0.11
	Enhanced or fortified waters	0.40	360	0.11
	Flavored or carbonated waters	0.40	360	0.11
	Non-milk-based nutritional and meal replacement beverages[c]	0.40	240	0.17
	Protein powder	0.40	360	0.11
Coffee and Tea	Instant coffee	0.40	360 (prepared)	0.11
	Specialty coffee drinks (including lattes, cappuccinos, mochas; RTD coffee drinks)	0.40	360	0.11
	Instant tea	0.40	360 (prepared)	0.11
	RTD tea beverages	0.40	360	0.11
Dairy Product Analogs	Milk substitutes (including imitation milk; soy milk and almond milk)	0.40	240	0.17
	Non-dairy cream	0.40	15	2.67
	Non-dairy yogurt	0.40	170	0.24
Fats and Oils	Margarine	0.40	15	2.67
Frozen Dairy Desserts	Ice cream	0.40	130 (or 2/3 cup)[d]	0.31
	Frozen yogurt	0.40	90 (or 2/3 cup)[d]	0.44
	Other frozen milk desserts	0.40	129 (or 2/3 cup)[d]	0.31
Grain Products and Pastas	Protein and nutrition bars (including health bars and fiber bars)	0.40	40	1.00
	Cereal and granola bars	0.40	40	1.00
Milk Products	Milk-based beverages including flavored milk beverage mixes; milks including chocolate milk, fruit milks, smoothies[c]	0.40	240	0.17
	Cocoa beverages[c]	0.40	240	0.17
	Milk-based nutritional and meal replacement beverages[c]	0.40	240	0.17
	Yogurt	0.40	170	0.24
	Yogurt drinks	0.40	93 to 207[e]	0.19 to 0.43

Table 1.4-1 Summary of the Individual Proposed Food Uses and Use Levels for Water-Soluble Palm Fruit Extracts in the U.S.

Food Category (21 CFR §170.3) (U.S. FDA, 2020)	Proposed Food Uses[a]	wsPFE Use Levels (g/serving), as consumed	RACC[b] (g or mL)	wsPFE Use Levels (g/100 g), as consumed
	Fermented milks	0.40	240	0.17
Nut and Nut Products	Processed nuts, coated nuts, nut mixtures	0.40	30	1.33
Processed Fruits and Fruit Juices	Fruit juices and nectars[c]	0.40	240	0.17
	Fruit drinks and ades[c]	0.40	360	0.11
Processed Vegetables and Vegetable Juices	Vegetable juices and blends	0.40	240	0.17
Soft Candy	Chocolate	0.40	30	1.33
	Gummies	0.40	30	1.33
Sugar Substitutes	Sugar Substitutes (powder and liquid)	0.40	1 to 4[f]; An amount equivalent to one reference amount for sugar in sweetness	10.00 to 40.00
Sweet Sauces, Toppings, and Syrups	Cocoa syrup	0.40	30	1.33

CFR = *Code of Federal Regulations*; RACC = Reference Amounts Customarily Consumed per Eating Occasion; RTD = ready-to-drink; U.S. = United States; wsPFE = water-soluble palm fruit extract.

[a] wsPFE is intended for use in unstandardized products where standards of identity, as established under 21 CFR §130 to 169, do not permit its addition in standardized products.

[b] Serving sizes based on the U.S. FDA RACCs (21 CFR §101.12 – U.S. FDA, 2020). RACCs are included for reference – the assessment was conducted based on use levels indicated on a percentage basis (g/100 g).

[c] Includes RTD and powders/concentrates.

[d] Calculated based on food item density using unit converter (https://www.aqua-calc.com/calculate/food-volume-to-weight)

[e] RACC has not been established for yogurt drinks; however, an approximate serving size was established based on products currently on the U.S. market.

[f] Approximate serving size was established based on products currently on the U.S. market.

1.5 Basis for GRAS

Pursuant to 21 CFR § 170.30(a)(b) of the *Code of Federal Regulations* (CFR) (U.S. FDA, 2020), the MPOB has concluded that the intended uses of wsPFE as described herein are GRAS on the basis of scientific procedures.

1.6 Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. FDA upon request, or will be available for review and copying at reasonable times at the offices of:

Malaysian Palm Oil Board
6, Persiaran Institusi
Bandar Baru Bangi
43000 Kajang
Selangor, Malaysia

Should the FDA have any questions or additional information requests regarding this Notification, the MPOB will supply these data and information upon request.

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

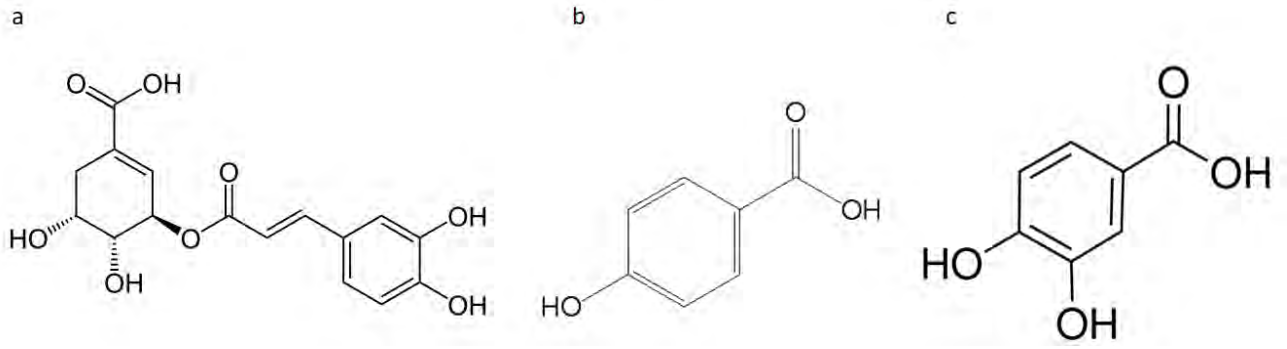
It is the MPOB's view that all data and information presented in Parts 2 through 7 of this Notice do not contain any trade secret, commercial, or financial information that is privileged or confidential, and therefore, all data and information presented herein are not exempted from the *Freedom of Information Act*, 5 U.S.C. 552.

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

2.1 Identity

The wsPFE is manufactured from the oil palm (*Elaeis guineensis*) plant from the family Arecaceae using a series of mechanical processes without the use of solvents or processing aids. Proximate analysis has been conducted on the ingredient and the results demonstrate that the ingredient is primarily comprised of carbohydrates (*ca.* 56%) and ash (*ca.* 26%), with the remaining components being protein (*ca.* 12%) and moisture (*ca.* 5%). The wsPFE ingredient contains a small amount (*ca.* 3.6%) of polyphenolic compounds such as caffeoylshikimic acid, p-hydroxybenzoic acid, and protocatechuic acid (Sambanthamurthi *et al.,* 2011a). Further details on the composition of the wsPFE are provided in Section 2.4. The chemical structures of the polyphenolic components of wsPFE are provided in Figure 2.1-1.

Figure 2.1-1 Chemical Structure of (a) Caffeoylshikimic Acid, (b) p-Hydroxybenzoic Acid, and (c) Protocatechuic Acid

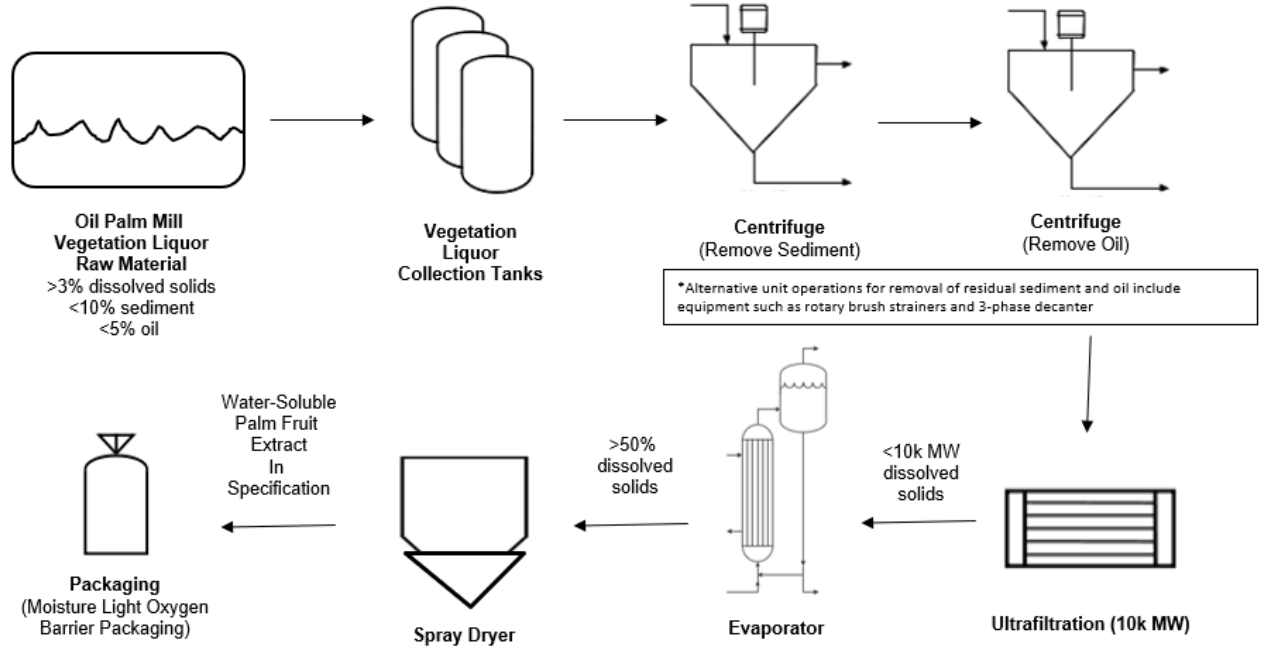


2.2 Manufacturing

The wsPFE ingredient is manufactured from the aqueous stream obtained during the milling of fresh whole palm fruit with the kernel removed from the oil palm (*E. guineensis*) that is processed using a series of mechanical means without the use of solvents or processing aids. These mechanical processes include heat exchange, filtration, centrifugation, ultrafiltration, and reverse osmosis. These physical refining steps are intended to remove undissolved solids, oleaginous parts, colloids, and higher weight molecules from the aqueous stream (vegetation liquor) thus yielding a refined aqueous fraction containing phytochemicals (*e.g.,* flavonoids, phenolic acids, and hydroxyl acids). In the first step of production, the starting material, vegetation liquor obtained from the aqueous stream of the milling of oil palm fruit, is centrifuged twice to remove any remaining sediment and oil, then the solution is passed through an ultrafiltration unit in which compounds greater than 10 kDa are removed. Next, the solution is evaporated to further remove any dissolved solids, and finally, the solution is spray-dried to yield the final wsPFE powder. A schematic of the manufacturing process is provided in Figure 2.2-1.

The production process of wsPFE incorporates a Hazard Analysis Critical Control Point (HACCP) system and will include appropriate preventative controls in accordance with the *Food Safety Modernization Act* (FSMA). The production process incorporates a food safety plan as part of the company's U.S. FDA-compliant current Good Manufacturing Practice (cGMP) quality management system, and incorporates a decision tree approach for evaluating any potential biological, chemical, and physical hazards throughout the manufacturing process flow. Furthermore, the food safety plan includes preventative controls for food allergens, sanitation, and supply chain, and a recall plan. The manufacturing process has been described in publicly available patents (PI98004378, US7387802, US8309145, and PCT/MY2014/000122). The raw material and food contact materials used in the production of wsPFE are food grade or equivalent, and are used in accordance with an applicable U.S. FDA regulation (*e.g.,* 21 CFR), have been previously determined to be GRAS, or have been the subject of an accepted food contact notification.

Figure 2.2-1 Schematic Overview of the Manufacturing Process for the Water-Soluble Palm Fruit Extract



2.3 Product Specifications

Food-grade specifications have been established for the wsPFE ingredient (on a dry weight basis) (see Table 2.3-1). All analytical methods used are internationally recognized [*e.g.,* Association of Official Analytical Chemists (AOAC) or United States Pharmacopeia (USP)].

Table 2.3-1 Product Specifications for Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Method of Analysis
Proximate		
Carbohydrates	≤60%	Calculated
Protein	≤15%	AOAC 968.06 AOAC 992.15 Dumas Method
Moisture	<8%	AOAC 925.09 AOAC 926.08

Table 2.3-1 Product Specifications for Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Method of Analysis
Ash	≤30%	AOAC 923.03
Total Polyphenols	≥3%	Folin-Ciocalteu Method
Heavy Metals		
Arsenic	≤1 ppm	ICP-MS
Cadmium	≤0.5 ppm	ICP-MS
Lead	≤0.5 ppm	ICP-MS
Mercury	≤25 ppb	ICP-MS
Microbiological Parameters		
Aerobic Plate Count	≤10,000 CFU/g	USPC2021
Escherichia coli	Negative per 10 g	USPE2022
Salmonella	Negative per 10 g	USPS2022
Staphylococcus aureus	Negative per 10 g	USPA2022
Yeast	≤100 CFU/g	USPM2021
Mold	≤100 CFU/g	USPM2021

AOAC = Association of Official Analytical Chemists; CFU = colony-forming units; ICP-MS = inductively-coupled plasma mass spectroscopy; ppb = parts per billion; ppm = parts per million; USP = United States Pharmacopeia.

2.4 Product Analysis

2.4.1 Proximate Analysis

The proximate composition of wsPFE was characterized up to 100% (see Table 2.4.1-1). The wsPFE ingredient is comprised primarily of carbohydrates (*ca.* 56%), protein (*ca.* 12%), moisture (*ca.* 5%), and ash (*ca.* 26%). The remaining component comprises polyphenolic compounds (mainly caffeoylshikimic acid, p-hydroxybenzoic acid, and protocatechuic acid). The total content of the major phenolic acids is approximately 3.6% of the product. Analytical data from 5 production lots of the wsPFE ingredient demonstrate that the manufacturing process previously described in Section 2.2 produces a consistent product that meets the product specifications.

Table 2.4.1-1 Summary of the Proximate Analysis for 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Manufacturing Lot							
		MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Carbohydrates (%)	≤60	54.2	56.5	55.6	58.1	57.2	56.3	±	1.34
Protein (%)	≤15	10.7	11.0	12.0	12.2	12.1	11.6	±	0.62
Moisture (%)	<8	6.45	7.72	4.58	4.01	4.27	5.41	±	1.44
Ash (%)	≤30	28.7	24.7	27.7	25.6	26.3	26.6	±	1.44
Total Polyphenols[a] (%)	≥3	3.44	3.42	3.97	3.66	3.61	3.62	±	0.20
Total Dietary Fiber[b] (%)	N/A	4.28	7.00	6.17	9.73	7.42	6.92	±	1.77
Total[c] (%)		**100.05**	**99.92**	**99.88**	**99.91**	**99.87**	**99.93**		

N/A = not available; SD = standard deviation.
[a] As gallic acid equivalents.
[b] Soluble and insoluble fiber.

Table 2.4.1-1 Summary of the Proximate Analysis for 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Manufacturing Lot							
		MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD

[c] Sum of carbohydrates, protein, moisture, and ash content.

2.4.2 Heavy Metals

Five production lots of the wsPFE ingredient were analyzed for potential heavy metals that may be present in the final product. A summary of the results of the analyses are provided in Table 2.4.2-1 below. Levels of arsenic (total), cadmium, and lead were all detectable at levels well below the respective specification limits, while mercury was not detected (limit of detection = 5 ppb) in any batch of wsPFE by inductively-coupled plasma mass spectroscopy (ICP-MS). All methods of analysis are internationally recognized or equivalent (*e.g.*, AOAC).

Table 2.4.2-1 Summary of the Heavy Metal Analysis of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Manufacturing Lot							
		MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Arsenic (ppm)	≤1.0	0.230	0.190	0.229	0.278	0.301	0.246	±	0.04
Cadmium (ppm)	≤0.5	0.164	0.140	0.146	0.137	0.18	0.153	±	0.02
Lead (ppm)	≤0.5	0.060	0.100	0.156	0.089	0.116	0.104	±	0.03
Mercury (ppb)	≤25	<5.0	<5.0	<5.0	<5.0	<5.0			

N/A = not available; ppm = parts per million; ppb = parts per billion; SD = standard deviation.

2.4.3 Mineral Content

Five production lots of wsPFE were analyzed for their mineral content. A summary of the analyses is presented in Table 2.4.3-1 below. The analytical data indicate the wsPFE ingredient contains measurable amounts of minerals, specifically calcium, iron, potassium, sodium, copper, magnesium, manganese, phosphorus, and zinc. The presence of these minerals in the final product account for the high ash content (*ca.* 26%) of wsPFE. The safety of these minerals based on the dietary exposures to the wsPFE ingredient is discussed in Section 3.1.5.

Table 2.4.3-1 Summary of the Mineral Content of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Manufacturing Lot							
	MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Calcium (ppm)	11,100	9,700	9,920	10,100	11,100	10,384	±	598
Iron (ppm)	1,290	1,380	1,270	1,130	1,580	1,330	±	148
Potassium (ppm)	120,000	95,000	105,000	89,200	92,400	100,320	±	11,170
Sodium (ppm)	1,650	1,290	1,210	622	854	1,125	±	357
Copper (ppm)	1.92	9.63	8.07	14.6	6.04	8.05	±	4.17
Magnesium (ppm)	22,900	20,200	17,700	19,100	18,600	19,700	±	1,792
Manganese (ppm)	135	175	189	179	227	181	±	29

Table 2.4.3-1 Summary of the Mineral Content of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Manufacturing Lot							
	MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Phosphorus (ppm)	7,000	5,570	6,240	5,460	5,710	5,996	±	569
Zinc (ppm)	51.1	49.7	49.3	43.7	46.8	48.1	±	2.6

NA = not analyzed; ppm = parts per million; SD = standard deviation.

2.4.4 Microbiological Analysis

A summary of the microbiological analysis for 5 production lots of wsPFE is presented in Table 2.4.4-1. The results demonstrate the absence of microbiological contaminants that would be of safety concern in the final product. The methods of analysis for the microbiological contaminants were Chapters 2021 and 2022 of the United States Pharmacopeia.

Table 2.4.4-1 Summary of the Microbiological Analysis of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Specification Limit	Manufacturing Lot				
		MX5634	MX5661	MX28919A	MX29419A	MX31719A
Aerobic Plate Count (CFU/g)	≤10,000	870	2400	150	700	2100
Escherichia coli (Negative/10 g)	Negative	Absent	Absent	Absent	Absent	Absent
Salmonella (Negative/10 g)	Negative	Absent	Absent	Absent	Absent	Absent
Staphylococcus aureus (Negative/10 g)	Negative	Absent	Absent	Absent	Absent	Absent
Yeast (CFU/g)	≤100	<10	<10	<100	<100	<100
Mold (CFU/g)	≤100	<10	<10	<100	<100	<100

CFU = colony-forming units; NA = not analyzed.

2.4.5 Sugar Profile

The sugar profile of 5 production lots of wsPFE was analyzed. A summary of the results is presented in Table 2.4.5-1 below.

Table 2.4.5-1 Sugar Profile of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Manufacturing Lot							
	MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Fructose (%)	1.8	2.6	3	3.2	1.7	2.5	±	0.8
Glucose (%)	1.5	2.5	3.1	3.4	2.3	2.6	±	0.8
Sucrose (%)	0.9	2	3.3	3.7	1.8	2.3	±	0.6
Lactose (%)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1		
Maltose (%)	0.2	0.4	0.5	0.4	0.5	0.4	±	0.1

Table 2.4.5-1 Sugar Profile of 5 Production Lots of Water-Soluble Palm Fruit Extract

Specification Parameter	Manufacturing Lot							
	MX5634	MX5661	MX28919A	MX29419A	MX31719A	Mean	±	SD
Galactose (%)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1		
Total (%)	**4.4**	**7.5**	**9.9**	**10.7**	**6.3**	**7.76**	±	**1.5**

SD = standard deviation.

2.4.6 Residual Pesticides

Two non-consecutive lots of wsPFE (Batch No. OPP SRTG020817 15 and OPP SRTG17041706) were analyzed for the list of USP 561 pesticides. The results demonstrate the levels of these pesticides to be below each respective limit of detection.

2.5 Stability

The stability of wsPFE (Lot No. MIT20170601-MP-09) was investigated under 2 accelerated conditions: storage at 60±2°C and ambient humidity for 46 days and 69 days. The 46-day study period was equivalent to 2 years of real-time aging, while the 69-day study period was equivalent to 3 years of real-time aging. The results of the accelerated storage stability studies are presented in Table 2.5-1 below. The results indicate no significant changes in the product specifications of wsPFE after storage at 60±2°C for 46 or 69 days, equivalent to 2 or 3 years, respectively.

Table 2.5-1 Results of Water-Soluble Palm Fruit Extract (Lot No. MIT20170601-MP-09) After Storage Under Accelerated Conditions for 46 or 69 Days (Temperature: 60±2°C, Ambient Humidity)

Specification Parameter	Specification Limit	Timepoint		
		T=0	T=46 Days	T=69 Days
Ash (%)	≤30%	26.8	26.3	26.5
Calories (cal/100 g)	N/A	266	273	274
Total Carbohydrate (g/100 g)	≤60%	59.1	58.8	58.8
Protein (%)	≤15%	11.4	11.3	11.5
Moisture (%)	≤5%	2.76	3.58	3.18
Soluble Fiber (%)	N/A	2.41	3.34	3.01
Total Sugar (%)	N/A	14.3	13.3	12
Total Polyphenols (%)	≥3%	4.2	3.6	3.4
Staphylococcus aureus (/10 g)	Negative per 10 g	Absent	Absent	Absent
Aerobic Plate Count (CFU/g)	≤10,000 CFU/g	1,500	217	167
Escherichia coli (/10 g)	Negative per 10 g	Absent	Absent	Absent
Mold Count (CFU/g)	≤100 CFU/g	10	100	0
Yeast Count (CFU/g)	≤100 CFU/g	<10	<100	<100
Salmonella (/10 g)	Negative per 10 g	Absent	Absent	Absent

CFU = colony-forming units; N/A = not available.

Part 3. §170.235 Dietary Exposure

3.1 Estimated Intake of Water-Soluble Palm Fruit Extract

3.1.1 Methods

An assessment of the anticipated intake of wsPFE as an ingredient under the intended conditions of use (see Table 1.4-1) was conducted using data available in the 2017-2018 cycle of the U.S. National Center for Health Statistics' National Health and Nutrition Examination Survey (NHANES) (CDC, 2018a,b, 2021a,b; USDA, 2018, 2021). An abbreviated summary along with the pertinent results is presented herein. Furthermore, as wsPFE contains polyphenols, the anticipated intake of total polyphenols, as gallic acid equivalents (GAE), from wsPFE was calculated based on the reported polyphenol content of wsPFE.

The NHANES data are collected and released in 2-year cycles with the most recent cycle containing data collected in 2017-2018. Information on food consumption was collected from individuals *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2). Sample weights were incorporated with NHANES data to compensate for the potential under-representation of intakes from specific populations and allow the data to be considered nationally representative (CDC, 2018a,b; USDA, 2018). The NHANES data were employed to assess the mean and 90th and 95th percentile intakes of wsPFE for each of the following population groups:

- Young children, ages 1 to ≤2 years;
- Children, ages 2 to 5;
- Children, ages 6 to 11;
- Female teenagers, ages 12 to 19;
- Male teenagers, ages 12 to 19;
- Female adults, ages 20 and up;
- Male adults, ages 20 and up; and
- Total population (ages 2 years and older, and both gender groups combined).

Consumption data from individual dietary records, detailing food items ingested by each survey participant, were collated by computer and used to generate estimates for the intake of wsPFE by the U.S. population[1]. Estimates for the daily intake of wsPFE represent projected 2-day averages for each individual from Day 1 and Day 2 of NHANES 2017-2018; these average amounts comprised the distribution from which mean and percentile intake estimates were determined. Mean and percentile estimates were generated incorporating survey weights in order to provide representative intakes for the entire U.S. population. "*Per capita*" intake refers to the estimated intake of wsPFE averaged over all individuals surveyed, regardless of whether they consumed food products in which wsPFE is proposed for use, and therefore includes individuals with "zero" intakes (*i.e.*, those who reported no intake of food products containing wsPFE during the 2 survey days). "Consumer-only" intake refers to the estimated intake of wsPFE by those individuals who reported consuming food products in which the use of wsPFE is currently under consideration. Individuals were considered "consumers" if they reported consumption of 1 or more food products in which wsPFE is proposed for use on either Day 1 or Day 2 of the survey.

[1] Statistical analysis and data management were conducted in DaDiet Software (Dazult Ltd., 2018). DaDiet Software is a web-based software tool that allows accurate estimates of exposure to nutrients and to substances added to foods, including contaminants, food additives and novel ingredients. The main input components are concentration (use level) data and food consumption data. Data sets are combined in the software to provide accurate and efficient exposure assessments.

The estimates for the intake of wsPFE were generated using the use level indicated for each intended food use, as presented in Table 1.4-1, together with food consumption data available from the 2017-2018 NHANES dataset. The results of this assessment are presented in Section 3.1.2. Intake estimates for wsPFE were then used to calculate the resulting intakes of polyphenols. These estimates are presented in Section 3.1.3.

The percentage of consumers was high among all age groups evaluated in the current intake assessment; greater than 95.8% of the population groups consisted of consumers of food products in which wsPFE is currently proposed for use. The consumer-only estimates are more relevant to risk assessments, as they represent exposures in the target population; consequently, only the consumer-only intake results are discussed in detail herein.

3.1.2 Intake Estimates for Water-Soluble Palm Fruit Extract

Among the total population (2 years and older), the mean and 95th percentile intakes of wsPFE were estimated to be 1.4 and 3.5 g/day, respectively, or 21 and 59 mg/kg body weight/day, respectively (see Table 3.1.2-1). Of the individual population groups, male adults were determined to have the greatest mean and 95th percentile intakes of wsPFE on an absolute basis, at 1.6 and 3.9 g/person/day, respectively, equivalent to 18 and 46 mg/kg body weight/day, respectively. Young children aged 1 to ≤2 years had the lowest mean and 95th percentile consumer-only intakes of 0.6 and 1.4 g/day, respectively, equivalent to 53 and 141 mg/kg body weight/day, respectively.

Table 3.1.2-1 Summary of the Estimated Daily Intake of Water-Soluble Palm Fruit Extract from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	Age Group (Years)	%	n	Consumer-Only Intake (g/day)			Consumer-Only Intake (mg/kg bw/day)		
				Mean	90th Percentile	95th Percentile	Mean	90th Percentile	95th Percentile
Young Children	1 to ≤2	92.6	147	0.6	1.2	1.4	53	101	141
Children	2 to 5	99.0	462	0.9	1.6	1.9	51	94	111
Children	6 to 11	99.4	672	1.0	1.8	2.1	32	59	70
Female Teenagers	12 to 19	96.0	431	1.0	1.8	2.4	17	33	41
Male Teenagers	12 to 19	98.2	431	1.1	2.3	2.9	18	37	51
Female Adults	20 and up	97.9	2,104	1.4	2.7	3.6	19	36	52
Male Adults	20 and up	96.6	1,914	1.6	3.1	3.9	18	37	46
Total Population	2 and up	97.5	6,014	1.4	2.6	3.5	21	44	59

bw = body weight; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

3.1.3 Intake Estimates for Water-Soluble Palm Fruit Extract as Gallic Acid Equivalents

A summary of the estimated daily intake of wsPFE on a GAE basis is provided in Table 3.1.3-1. Total daily intakes of polyphenols as GAE were calculated from wsPFE intake estimates (see Section 3.1.2), assuming wsPFE contains an average of 3.6% total polyphenols as GAE, based on the results of 5 production batches of wsPFE (see Table 2.4.1-1).

Among the total population (2 years and older), the mean and 95th percentile intakes of polyphenols as GAE from the proposed uses of wsPFE were estimated to be 49 and 124 mg/day, respectively. Male adults were estimated to have the highest mean and 95th percentile intakes of GAE on an absolute basis of 57 and 141 mg/day, respectively. The young children group aged 1 to ≤2 years had the lowest mean and 95th percentile intakes of 21 and 50 mg/day, respectively.

Table 3.1.3-1 Summary of the Estimated Daily Intake of Water-Soluble Palm Fruit Extract as Gallic Acid Equivalents[a] from Proposed Food Uses in the U.S. by Population Group (2017-2018 NHANES Data)

Population Group	Age Group (Years)	%	n	Consumer-Only Intake (mg GAE/day)			Consumer-Only Intake (mg GAE/kg bw/day)		
				Mean	90th Percentile	95th Percentile	Mean	90th Percentile	95th Percentile
Young Children	1 to ≤2	92.6	147	21	42	50	1.9	3.6	5.1
Children	2 to 5	99.0	462	31	59	69	1.8	3.4	4.0
Children	6 to 11	99.4	672	37	65	76	1.2	2.1	2.5
Female Teenagers	12 to 19	96.0	431	37	66	86	0.6	1.2	1.5
Male Teenagers	12 to 19	98.2	431	41	84	104	0.7	1.3	1.8
Female Adults	20 and up	97.9	2,104	50	95	131	0.7	1.3	1.9
Male Adults	20 and up	96.6	1,914	57	112	141	0.6	1.3	1.7
Total Population	2 and up	97.5	6,014	49	95	124	0.8	1.6	2.1

bw = body weight; GAE = gallic acid equivalents; NHANES = National Health and Nutrition Examination Survey; U.S. = United States.

[a] Calculated using average GAE content of 3.6%.

3.1.4 Background Intakes of Polyphenols

Polyphenols categorized mainly as flavonoids, phenolic acids, lignans, and stilebenes, are a large class of compounds that are widely distributed in foods (Chiva-Blanch and Badimon, 2017; Del Bo *et al.,* 2019). The major sources of polyphenols in food were reported to be wine, beer, coffee, tea, cocoa, vegetables, fruits, and nuts. The phenolic acid subclass includes hydroxybenzoic acid, protocatechuic acid, and caffeoylshikimic acid (caffeic acid derivative), which are present in the wsPFE ingredient (see Section 2.1). The background dietary intakes of polyphenols from their natural occurrences in food were previously discussed in GRN 497, which received no questions from the U.S. FDA (Amino Up Chemical Co., Ltd., 2013; U.S. FDA, 2014). In GRN 497, the Applicant noted that consumption of the recommended 5 servings of fruits and vegetables per day would provide over 500 mg of polyphenols (Williamson and Holst, 2008; Martin and Appel, 2010). The total intake of total polyphenols from the typical diet is estimated to range from 100 to over 2,000 mg/day (Clifford, 2004). The Applicant concluded that consumption of a normal balanced diet may provide approximately 1,000 mg/day of polyphenols (Amino Up Chemical Co., Ltd., 2013). Based on a recent search of the scientific literature, the estimated dietary intakes of polyphenols in the U.S. population are in the range of approximately 900 mg/day (Del Bo *et al.,* 2019) or up to 884±20 mg per 1,000 kcal/day, equivalent to up to 1,000 mg/day for phenolic acids (Huang *et al.,* 2020), which is consistent with previous conclusions from GRN 497.

As outlined above, the estimated intake of wsPFE in the total population based on the intended uses is 3.5 g/day (95th percentile), which will provide approximately 124 mg/day of polyphenols as GAE to the diets of the U.S. population. In male adults, the proposed food uses of wsPFE would provide approximately 141 mg GAE/day. The reported no-observed-adverse-effect level (NOAEL) for the wsPFE product containing 4.4% polyphenols from the 90-day repeated-dose oral toxicity study in rats is 2,000 mg/kg body weight/day. This NOAEL supports an approximate polyphenol intake of 6.2 g as GAE/day for a 70-kg individual. Therefore, the level of polyphenol intake from the intended uses of wsPFE are not expected to pose a safety concern in the U.S. population.

3.1.5 Estimated Exposure to Minerals

The exposure to various minerals present in the wsPFE ingredient has been assessed based on the highest 95th percentile intakes of wsPFE on an absolute basis, presented in Table 3.1.5-1. Based on the mean concentrations of the various minerals present in the wsPFE ingredient (see Table 2.4.3-1) and the estimated intakes of wsPFE in male adults at the 95th percentile (see Table 3.1.2-1), the highest consumption group, the intakes of these minerals in male adults were well below the established tolerable upper limits proposed by the European Food Safety Authority (EFSA) and the Institute of Medicine (IOM). Therefore, intakes of minerals resulting from the use of wsPFE as a food ingredient is not associated with any toxicological concern.

Table 3.1.5-1 Estimated Exposure to Minerals from Water-Soluble Palm Fruit Extract in Male Adults (95th Percentile)

Mineral	Exposure in Male Adults	Tolerable Upper Limit in Adults (EFSA, 2018)	Tolerable Upper Limit in Male Adults (IOM, 2006)
Calcium	40.5 mg/day	2,500 mg/day	2,500 mg/day (19 to 50 y) 2,000 mg/day (51 to >70 y)
Copper	0.03 mg/day	5 mg/day	10,000 µg/day
Iron	5.2 mg/day	N/A[a]	45 mg/day
Magnesium	76.8 mg/day	250 mg/day	350 mg/day
Manganese	0.7 mg/day	N/A[a]	11 mg/day
Phosphorus	23.4 mg/day	N/A[a]	4 g/day (19 to 70 y) 3 g/day (>70 y)
Potassium	391 mg/day	N/A[a]	N/A[b]
Sodium	4.3 mg/day	N/A[a]	N/A[b]
Zinc	0.2 mg/day	25 mg/day	40 mg/day

N/A = not available; y = years.
[a] No adequate data is available to derive an upper limit.
[b] Not determined due to a lack of a specific toxicological effect.

3.1.6 Estimated Exposure to Arsenic

The estimated dietary exposure to arsenic from the proposed uses of wsPFE were calculated based on the average arsenic content of 0.25 ppm across 5 production batches of wsPFE (see Table 2.4.2-1) and the estimate daily intakes of wsPFE from Section 3.1.2. Based on the proposed food uses of wsPFE, the arsenic exposure in the total U.S. population (ages ≥2 years) is approximately 0.005 µg/kg body weight/day (mean) or 0.015 µg/kg body weight/day (95th percentile). Young children (1 to ≤2 years) had the highest arsenic exposure of 0.013 µg/kg body weight/day (mean) or 0.035 µg/kg body weight/day (95th percentile). In comparison, the background intake of total arsenic and inorganic arsenic in the U.S. population was

reviewed by JECFA (2011) and discussed in 4 publications (Schoof *et al.,* 1999; Meliker *et al.,* 2007; Tsuji *et al.,* 2007; Xue *et al.,* 2010). The total arsenic exposure from food and water was reported to be up to 0.39 µg/kg body weight/day (mean) and 1.51 µg/kg body weight/day (95th percentile) in the total population, and up to 0.57 µg/kg body weight/day (mean) and 2.21 µg/kg body weight/day (95th percentile) in young children (1 to ≤2 years old) (Xue *et al.,* 2010). The results indicate the total arsenic exposure from the proposed food uses of wsPFE are significantly below the background arsenic exposure from the diet in the U.S. population. It should be noted that the dietary exposures to arsenic from the proposed uses of wsPFE were estimated at the mean and 95th percentile. This approach is considered to estimate the "worst-case" and accounts for several conservative assumptions, as discussed below in Section 3.1.7, and therefore the actual consumption of wsPFE will be considerably lower.

Table 3.1.6-1 Summary of the Estimated Daily Intake of Total Arsenic from the Proposed Food Uses of Water-Soluble Palm Fruit Extract

Population Group	Age Group (Years)	Daily Intake of wsPFE Proposed Food Uses (mg/kg bw/day)		Total Arsenic Intake from Proposed Food Uses of wsPFE (µg/kg bw/day)	
		Mean	95th Percentile	Mean	95th Percentile
Young Children	1 to ≤2	53	141	0.01325	0.03525
Children	2 to 5	51	111	0.01275	0.02775
Children	6 to 11	32	70	0.008	0.0175
Female Teenagers	12 to 19	17	41	0.00425	0.01025
Male Teenagers	12 to 19	18	51	0.0045	0.01275
Female Adults	20 and up	19	52	0.00475	0.013
Male Adults	20 and up	18	46	0.0045	0.0115
Total Population	2 and up	21	59	0.00525	0.01475

bw = body weight; NHANES = National Health and Nutrition Examination Survey; U.S. = United States; wsPFE= water-soluble palm fruit extract.

3.1.7 Summary and Conclusions

Consumption data and information pertaining to the intended food uses of wsPFE were used to estimate the consumer-only intakes of this ingredient for specific demographic groups and the total U.S. population. There were a number of assumptions included in the assessment which render exposure estimates suitably conservative. For example, it has been assumed in this exposure assessment that all food products within a food category contain wsPFE at the maximum specified level of use. In reality, the levels added to specific foods will vary depending on the nature of the food product and it is unlikely that wsPFE will have 100% market penetration in all identified food categories.

In summary, the resulting mean and 95th percentile intakes of wsPFE by the total U.S. population (2 years and older) from the proposed food uses were estimated to be 1.4 g/day and 3.5 g/day, respectively, providing approximately 49 and 124 mg/day of polyphenols as GAE, respectively. Among the individual population groups, male adults were identified as having the highest absolute mean and 95th percentile intakes of wsPFE of 1.6 g/day (equivalent to 57 mg GAE/day) and 3.9 g/person/day (equivalent to 141 mg GAE/person/day), respectively. Although younger populations were identified as the groups having higher exposures to wsPFE on a body weight basis, and consequently polyphenols as GAE, it should be noted that products containing wsPFE will not be targeted towards children and estimates described herein assume *all* products, including those consumed by younger individuals, would contain the ingredient at the maximum intended use levels. In actuality, these products would, in the worst case, only be consumed incidentally,

and intakes of wsPFE described in the older populations are expected to be more accurate estimates of dietary exposure among the intended population.

The exposure to various minerals and arsenic present in the wsPFE ingredient was assessed based on the mean concentrations of the various minerals and arsenic present in the wsPFE and the highest estimated intake of wsPFE at the 95th percentile, as observed in male adults. The intakes of these minerals were determined to be well below the established tolerable upper limits proposed by EFSA and the IOM and are, therefore, not expected to be associated with any toxicological concern. The intakes of arsenic based on the proposed food uses of wsPFE are well below the background intakes of arsenic in the U.S. population and are not expected to pose a safety concern.

Part 4. §170.240 Self-Limiting Levels of Use

No known self-limiting levels of use are associated with wsPFE.

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

Not applicable.

Part 6. §170.250 Narrative and Safety Information

6.1 Introduction

The wsPFE ingredient is derived from fruit of the oil palm tree (*Elaeis guineensis*), an ancient tropical plant that originated from West Africa (Clemens *et al.,* 2017). As discussed in Section 3.2, the wsPFE ingredient is derived from the aqueous stream obtained during the milling of the oil palm fruit that is subject to a series of mechanical processing steps that do not require the use of any solvents or processing aids. A comprehensive search of the scientific literature was conducted using the electronic search tool ProQuest™ to identify studies reporting on the metabolic fate [*i.e.*, absorption, distribution, metabolism, and excretion (ADME)] and safety outcomes for wsPFE. The search was conducted through April 2021 using the following databases: Adis Clinical Trials Insight, AGRICOLA, AGRIS, Allied & Complementary Medicine™, BIOSIS® Toxicology, CAB ABSTRACTS, Embase®, Foodline®: SCIENCE, FSTA®, MEDLINE®, and ToxFile®. No studies on the ADME of wsPFE were identified in the literature. The search identified a series of genotoxicity studies, including a bacterial reverse mutation test and an *in vitro* chromosomal aberration test, and a 90-day repeated-dose oral toxicity study in rats on the wsPFE ingredient (Lynch *et al.,* 2017). The results of these studies demonstrate the absence of mutagenicity and clastogenicity of the wsPFE ingredient and show no significant adverse effects in the 90-day toxicity study in rats. The results of these studies are discussed in further detail in Section 6.3 and serve as the pivotal data to support the safety of wsPFE. These studies were conducted in accordance with Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice (GLP) and respective OECD test guidelines for the toxicity testing of chemicals.

6.2 Absorption, Distribution, Metabolism and Excretion

Studies evaluating the ADME of wsPFE were not identified in the scientific literature. However, considering that the wsPFE ingredient is comprised primarily of carbohydrates, specifically monosaccharides and polysaccharides/oligosaccharides, it is expected that the metabolic fate of the ingredient will follow the normal metabolic pathway for these substances. Polysaccharides and oligosaccharides are typically not digested in the upper gastrointestinal tract and instead pass through undigested and are absorbed into the small intestine and transported to the colon where they are metabolized by anaerobic bacteria. The anaerobic microorganisms that inhabit the colon break down these polysaccharides and oligosaccharides to yield short-chain fatty acids such as butyric acid, acetic acid, and propionic acid, and innocuous gases such as methane, carbon dioxide, and hydrogen gas.

6.3 Toxicological Studies

Several toxicological studies investigating the safety of OPP as produced by the MPOB were identified in the scientific literature. These studies included:

1. A short-term oral toxicity study in mice provided OPP in the drinking water at levels equivalent to 1,500 mg/kg GAE for 6 weeks in which no significant changes in organ weights and histology, food or fluid intake or standard hematology and clinical chemistry parameters were noted (Leow *et al.,* 2011, 2013); and

2. A 3-generation teratogenicity study in Sprague-Dawley rats provided OPP in the drinking water at levels of 1,500 or 2,400 mg/L GAE in which no significant effects in any generation were reported that would indicate a safety concern (Sambanthamurthi *et al.,* 2011a).

In addition to these studies, a 90-day oral toxicity study conducted in rodents and a standard battery of assays evaluating the mutagenicity and genotoxicity of wsPFE as produced by the MPOB were published in the scientific literature (Lynch *et al.,* 2017). The bioassays described by Lynch *et al.* (2017) were all conducted in accordance with appropriate GLP and OECD test guidelines (*e.g.,* OECD Test Guideline 471, 473, and 408) (OECD, 1997, 1998a, 2014). The test article utilized in these studies were compositionally similar to the wsPFE ingredient described herein (see Table 6.3-1 for comparison of the test articles). Furthermore, a series of studies conducted in rodents consuming PFJ, a derivative of the oil palm tree, for up to 36 weeks was identified (Bolsinger *et al.,* 2014). In addition to these safety-related studies, several studies were identified evaluating the efficacious effects of OPP at levels up to 3,000 ppm GAE in the drinking water for up to 17 weeks (Sambanthamurthi *et al.,* 2011a,b). These efficacious endpoints included effects on blood pressure, cardiovascular effects, atherosclerosis, and anti-diabetic effects, and are included for completeness. These studies are discussed in further details in the sections that follow.

It is noted that these substances (*i.e.,* wsPFE, wsPFB, PFJ, OPP) were all produced by the MPOB using the same production method as described in Section 2.2, and are synonymous. The study by Lynch *et al.* (2017) served as the pivotal study to support the safety of wsPFE as it was conducted in accordance with appropriate toxicology test protocol and GLP, and as shown in Table 6.3-1, was compositionally similar to the ingredient described herein.

Table 6.3-1 Comparison of the Test Materials Utilized in the Toxicological Studies

Parameter	wsPFE[a] (as described herein)	wsPFB[b] (Lynch *et al.,* 2017)	Palm Fruit Juice[c] (Bolsinger *et al.,* 2014)
Carbohydrates	56%	*ca.* 60%	65% (mainly sucrose and fiber)
Protein	11.6%	*ca.* 10%	12%
Ash	26.6%	*ca.* 20%	20%
Moisture	5.4%	*ca.* 8%	NR
Polyphenols	3.6%	*ca.* 4 to 5% (as GAE)	*ca.* 3.5%

GAE = gallic acid equivalents; NR = not reported; wsPFB = water-soluble palm fruit bioactives; wsPFE = water-soluble palm fruit extract.

[a] Mean values of 5 production lots of wsPFE.

[b] Powder form.

[c] Liquid form.

6.3.1 Repeated-Dose Oral Toxicity Studies

6.3.1.1 Studies Conducted with Water-Soluble Palm Fruit Extract

The systemic toxicity of wsPFE was investigated in Crl:CD(SD) Sprague-Dawley rats conducted in accordance with OECD Test Guideline 408, United Kingdom GLP Regulations, OECD Principles of GLP, and European Commission Directive 2004/10/EC (OECD, 1998a,b; EC, 2004). Animals (10/sex/group) were administered wsPFE by gavage at doses of 0, 500, 1,000, or 2,000 mg/kg body weight/day for 90 days. The phenolic acid content of the test article was reported to be approximately 4 to 5% as GAE; thus the doses of wsPFE provided 0, 25, 50, or 100 mg GAE/kg body weight/day. The control animals received the vehicle only (distilled water). Homogeneity and stability of the test substance were confirmed to be appropriate for the study duration. The doses used in the study were established based on a 28-day range finding toxicity test. In this study, conducted in the same strain of rat, no evidence of overt toxicity was noted at the highest dose tested of 2,000 mg/kg body weight/day (Lynch *et al.,* 2017).

Detailed clinical observations were recorded weekly. Ophthalmologic examinations were performed on all animals both before the study and during Study Week 12. Body weights and food consumption were recorded weekly. A functional observational battery (FOB) was conducted near the end of the study. Blood samples for hematology and blood biochemistry were collected during the final week of the study. A standard range of parameters required as per OECD guidelines was measured. All animals were subject to a terminal necropsy with macroscopic observation. The weights of the following organs were measured: adrenals (combined), brain, epididymides, heart, kidneys (combined), liver, ovaries, testes (combined), spleen, thymus, thyroid gland, and uterus with cervix. Samples of these and all other standard OECD test protocol organs were collected for histopathological examination.

Treatment with wsPFE was not associated with any mortality or overt clinical signs. Likewise, throughout the course of the study, there was no substantive effect of wsPFE treatment on body weight or body weight gain although overall body weight gain by males receiving 2,000 mg/kg body weight/day was slightly (approximately 10%) lower than that of the controls, however, this difference was not statistically significant and there was no similar trend in the females. Also, in males at the high-dose, there was a decrease in food consumption in comparison to controls during the treatment period. No biologically relevant effects of treatment were noted on the results of the FOB; however, a significant increase in forelimb grip strength was observed in females receiving 2,000 mg/kg body weight/day compared to the controls (0.93, 0.95, 0.91, and 0.99 kg in control through high-dose females, respectively), but the magnitude of the difference was small, no clear dose-response relationship was observed, and the mean value for these animals was within the range of historical control data from the laboratory. Additionally, no significant differences in motor activity were reported. Treatment with wsPFE did not alter the results of the ophthalmological examinations. Likewise, there were no significant effects in hematological or biochemical evaluations that were considered adverse. Significant decreases in mean corpuscular hemoglobin concentrations (MCHC) in males and in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities and bile acid concentrations in females receiving 2,000 mg/kg body weight/day, compared to the controls, were reported. Significantly increased mean MCHC in females receiving 1,000 and 2,000 mg/kg body weight/day and significantly increased mean corpuscular hemoglobin in females, compared to the controls, were also reported. These effects were not considered adverse due to the small magnitude of the effects, inconsistent findings across sexes, no clear dose-response relationship, and the effects were within the range of historical control data from the laboratory. Furthermore, no significant effects were observed in red blood cell counts, total hemoglobin or hematocrit concentrations, or associated findings in histopathological examinations that would indicate that these effects would be adverse. At necropsy, there was no observable effect of treatment on the incidence of visible lesions and the results of the organ weight analysis revealed no adverse effects of treatment with wsPFE. While the absolute and relative weights of the uterus in animals was slightly, but significantly decreased at the 1,000 or 2,000 mg/kg body weight/day dose levels, there were no histopathological correlates. No treatment-related histopathological changes were noted.

Based on the results of this study, the study authors concluded that the NOAEL was 2,000 mg/kg body weight/day, the highest dose tested.

6.3.1.2 Studies Conducted with Palm Fruit Juice (PFJ)

The anti-diabetic effects of PFJ containing OPP was evaluated in the Nile rat (*Arvicanthis niloticus*) (Bolsinger *et al.,* 2014). The PFJ used in this study was comparable to the wsPFE ingredient used in the 90-day oral toxicity study by Lynch *et al.* (2017) and the wsPFE ingredient that is the subject of this Notice (see Table 6.3-1). The Nile rat was utilized in this study as it is a novel model for carbohydrate-induced type 2 diabetes and metabolic syndrome. Wild-type male Nile rats (n=100) were separated into different groups for 5 separate experiments as shown in Table 6.3.1.2-1 below. The OPP content of the PFJ was measured as GAE by spectrophotometric assay. The study parameters that were evaluated included food and fluid intake, body weight, and random and fasting blood glucose at different timepoints. The terminal fasting organ weights, insulin analysis, and plasma and liver lipids were also measured as markers of diabetes progression.

Table 6.3.1.2-1 Summary of the Experiments Conducted in Nile Rats with Palm Fruit Juice (Bolsinger *et al.,* 2014)

Experiment	Study Groups	Experimental Conditions	Endpoints
1. Purpose: To test the anti-diabetogenic qualities of PFJ	N=16 (8/group) Age: 12 weeks	Duration: 36 weeks Diet: Standard laboratory chow *ad libitum* Treatment: Water or PFJ containing 1,500 mg GAE/L (equivalent to consumption of 648 mg GAE/kg bw/day)	• Food and fluid intakes • Body weight • Fasting and random blood glucose • Plasma lipid and insulin analyses • Liver lipids • Organ weights
2. Purpose: To assess the relationship between phenolic content of PFJ and its anti-diabetogenic effect	N=27 (6 or 7/group) Age: 12 weeks	Duration: 17 weeks Diet: Standard laboratory chow *ad libitum* Treatment: PFJ in drinking water at levels providing 0, 450, 900, or 1,800 mg GAE/L (equivalent to consumption of 0, 170, 360, 627 mg GAE/kg bw/day, respectively)	• Food and fluid intakes • Body weight • Fasting blood glucose • Plasma lipid and insulin analyses • Liver lipids • Organ weights
3. Purpose: To assess the effectiveness of providing PFJ blended directly in a semi purified diet	N=23 (11 or 12/group) Normoglycemic rats Age: 8 weeks	Duration: 24 weeks Treatment: Control diet (moderate CHO and fat) or PFJ in the diet at levels providing 5.4 g GAE/kg dry diet (equivalent to consumption of 409 mg GAE/kg bw/day)	• Body weight • Random blood glucose • Plasma lipid and insulin analyses • Liver lipids • Organ weights
4. Purpose: To test the possibility of reversing diabetes with PFJ	N=10 (5/group) Pre-existing random hyperglycemic rats Age: 12 weeks	Duration: 6 weeks Treatment: Control diet (moderate CHO and fat) or PFJ in the diet at levels providing 10.4 g GAE/kg dry diet (equivalent to consumption of 545 mg GAE/kg bw/day)	• Food and drink intakes • Body weight • Plasma lipid and insulin analyses • Liver lipids • Organ weights

Table 6.3.1.2-1 Summary of the Experiments Conducted in Nile Rats with Palm Fruit Juice (Bolsinger *et al.,* 2014)

Experiment	Study Groups	Experimental Conditions	Endpoints
5. Purpose: To compare application method (drink *vs*. diet) within the same study	N=23 (7 or 8/group) Age: 3 weeks	Duration: 4 weeks Treatment Control Group: semi purified high CHO diet Experimental Group 1: semi purified high CHO diet plus unsweetened PFJ as a drink (273 mg GAE/kg bw/day) Experimental Group 2: semi purified high CHO diet with unsweetened PFJ in the diet (720 mg GAE/kg bw/day)	• Body weight • Fasting and random blood glucose • Plasma lipid and insulin analyses • Liver lipids • Organ weights

bw = body weight; CHO = carbohydrate; GAE = gallic acid equivalents; N = number; PFJ = palm fruit juice.

It was noted that the levels of consumption of PFJ in these studies were equivalent to doses up to 648 mg GAE/kg body weight/day in the drinking water (Experiments 1 and 2) or up to 720 mg GAE/kg body weight/day in the diet (Experiments 3, 4, and 5). The dosages of PFJ in this study provided significantly greater levels of GAE to rats than the study by Lynch *et al.* (2017), and thus it is difficult to ascertain whether the findings on the liver and kidney could be attributable to consumption of PFJ and polyphenols as GAE; therefore, it is difficult to extrapolate the results of this study to support the safety of the wsPFE ingredient. Overall, while no adverse effects were observed at any level of PFJ intake that would raise any safety concerns, the primary objective of this study was to investigate an efficacious effect of PFJ consumption, and therefore the utility of this study in the safety assessment of the wsPFE ingredient is limited.

6.3.2 Mutagenicity/Genotoxicity

6.3.2.1 Bacterial Reverse Mutation Assay (Ames Test)

The bacterial reverse mutation assay was performed in *Salmonella* Typhimurium TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA (Lynch *et al.,* 2017). The first experiment was conducted according to the plate incorporation method (Ames *et al.,* 1975), while the second experiment was conducted using the pre-incubation method (Maron and Ames, 1983). The purity of the wsPFE tested was 100%. In each experiment, wsPFE was tested at concentrations of 0, 5, 15, 50, 150, 500, 1,500, and 5,000 µg/plate in the first experiment for all tester strains and 0, 50, 150, 500, 1,500, and 5,000 µg/plate for all tester strains in the second experiment. The vehicle (water) served as the negative control. The positive controls included in the absence of S9 mix: 2 µg/plate 2-nitrofluroene, 2 µg/plate sodium azide, 50 µg/plate 9-aminoacridine, 2 µg/plate 4-nitroquinoline-1-oxide; and in the presence of S9: 5 µg/plate benzo[a]pyrene, 5 µg/plate 2-aminoanthracene, 10 mg/plate 2-aminoanthracene. The S9 fraction was prepared from male Sprague-Dawley rats administered phenobarbital/5,6-benzoflavone to stimulate mixed-function oxidases in the liver.

For both the plate incorporation and the pre-incubation assays, no increases in the revertant colony numbers were observed in any of the 5 tester strains exposed to wsPFE at concentrations of up to 5,000 µg/plate, either in the presence or absence of metabolic activation. In comparison, the positive controls significantly increased the number of revertant colonies in each tester strain. All criteria for a valid assay were met. There was no evidence of toxicity of wsPFE to the tester strains as evidenced by the absence of changes to the background lawn. The authors concluded that the results of this study demonstrate that the phenolic acids and other compounds in the wsPFE do not have mutagenic activity.

6.3.2.2 In Vitro Chromosome Aberration Assay

The aneugenic and clastogenic potential of wsPFE was investigated in an *in vitro* mammalian chromosome aberration assay with human lymphocytes (Lynch *et al.,* 2017). This study was conducted in accordance with GLP and OECD Test Guideline 473 (OECD, 1998b, 2014). Human lymphocytes were obtained from 2 healthy non-smoking donors. In the preliminary assay, cells were treated for 3 or 21 hours in the absence of S9 or for 3 hours in the presence of S9 metabolic activation. wsPFE was tested at concentrations of 0, 50.39, 83.98, 139.97, 233.28, 388.8, 648, 1,080, 1,800, 3,000, and 5,000 µg/mL. Two hours before the cells were harvested, mitotic activity was ceased by addition of Colcemid® to each culture at a final concentration of 0.1 µg/mL. Samples were prepared for microscopic examination. The incidence of mitotic cells per 1,000 cells and mitotic index were assessed. In the main test, wsPFE was tested in duplicate at concentrations of 1,000, 2,000, 3,000, 4,000, and 5,000 µg/mL. Concentrations of 3,000, 4,000, and 5,000 µg/mL were selected for analysis for the 3-hour experiments and 1,000, 3,000, and 5,000 µg/mL for the 21-hour experiment. Chromosome aberrations were scored according to an established classification system (ISCN) (Shaffer *et al.*, 2009). Positive controls were included: mitomycin C (absence of S9) and cyclophosphamide (presence of S9).

No biologically significant increases in the incidence or percentage of cells with chromosome aberrations was observed as a result of treatment with wsPFE. In addition, wsPFE did not increase the occurrence of polyploidy (all values ≤1.0%) or endoreduplicated cells (all values = 0%). As expected, the positive controls caused significant increases in chromosome aberrations, and therefore, all aspects of this assay were considered to meet the validation criteria. Based on the results of this study, the study authors concluded that wsPFE does not have aneugenic or clastogenic potential in mammalian cells.

6.4 Human Studies

Two human clinical studies on OPP or a palm fruit bioactive complex derived from *E. guineensis* were identified in the literature (Fairus *et al.,* 2018; Hewlings and Kalman, 2020).

A Phase I single-blind crossover clinical trial was conducted with healthy subjects consuming placebo or OPP for 60 days (Fairus *et al.,* 2018). Twenty-five subjects (11 males, 14 females) were provided either 150 mL of a test or placebo drink (mineral water) twice daily for consumption for a period of 60 days. The test drink consisted entirely of the phenolic acid-containing product (referred to as PFJ) and was stated to contain phenolic acids at a level of 1,500 mg/L GAE, providing a daily intake of 450 mg GAE; however, no other details pertaining to the identity or specifications of the phenolic product administrated during this trial were provided. The first 60-day intervention period was followed by a 28-day wash-out period before the 2 groups switched interventions and continued the trial for another 60 days. On Days 30 and 60 of each intervention period, fasting blood (for lipid, endocrine, electrolyte, renal and liver function, high-sensitive C-reactive protein, glycosylated hemoglobin, and hematology analysis) and urine (for albumin and creatinine analysis) samples were collected from study participants and blood pressure (systolic and diastolic) and anthropometric (weight and height) measurements were taken. Blood sample analysis

revealed only a few significant variations between the control and test group values (higher red blood cell count on Day 30 and lower plasma total cholesterol and low-density-lipoprotein concentrations on Day 60 following consumption of the phenolic product-containing juice compared to control values). These changes were reported to be in the normal range according to standard clinical safety references. No significant changes in clinical biochemistry profiles were observed between treatment compared to placebo. No adverse effects, adverse events, or serious side effects were reported. The study authors concluded that consumption of OPP or PFJ at levels providing 450 mg GAE/day does not cause any safety concerns in humans.

In a pilot study conducted with a randomized, double-blind, placebo-controlled design, 29 physically active participants (13 males, 16 females, mean age of 39 years, mean body mass index of 29.1 kg/m^2) were provided with 0, 250, 500, or 1,000 mg palm fruit bioactive complex daily for 30 days (Hewlings and Kalman, 2020). No further details regarding the identity or form of the test material were provided. Body weight, body composition, heart rate variability, serum lipid profile (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides), serum cytokines [tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1B, MCP-1, IL-8], uric acid, and cardiac troponin were assessed prior to dosing and after the 30-day test period. No significant changes were reported for any of the measures or biomarkers between the treatment and placebo groups at the end of the study period. The authors concluded that all doses of the test material were safe and well-tolerated by subjects.

6.5 Allergenicity

As the wsPFE contains approximately 12% protein, there is a possibility that the ingredient may have potential to elicit allergenic reactions in final consumers. It is expected that the ultrafiltration step utilized in the production process of wsPFE would remove potential allergenic proteins in the wsPFE final product. A search of the literature was conducted to identify whether allergenic reactions have been reported following consumption and/or exposure to oil palm fruit. No results were identified in PubMed using the search terms "oil palm" and "allergen*". Likewise, a review of 3 major allergen databases, AllergenOnline[2], COMPARE[3], and WHO/IUIS allergen database[4], did not reveal any entries for putative allergens originating from oil palm or *Elaeis guineensis*. Based on the available information, no evidence exists that indicate that wsPFE would produce an allergenic response following consumption of foods to which the ingredient is added. Therefore, the use of wsPFE is not anticipated to pose any allergenicity concerns in consumers.

[2] AllergenOnline is an allergen protein database containing 2,129 peer-reviewed allergenic protein sequences (Version 19; released on February 10, 2019) that is curated by the Food Allergy Research and Resource Program (FARRP) of the University of Nebraska. The database is available at: http://www.allergenonline.org/.

[3] The COMprehensive Protein Allergen REsource (COMPARE) database is a manually-curated allergenic protein database maintained by the Health and Environmental Sciences Institute (HESI). The COMPARE database contains about 2,081 allergenic proteins in total. The database is available at: http://db.comparedatabase.org/.

[4] The WHO/IUIS allergen database contains 948 allergenic proteins and is maintained by the World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee. The database is available at: http://www.allergen.org/index.php.

6.6 Summary of the Safety Data

The safety of the wsPFE ingredient was assessed in a number of toxicological studies in mice and rats (Leow *et al.*, 2011, 2013; Sambanthamurthi *et al.,* 2011a,b; Lynch *et al.,* 2017). These studies provided OPP in the drinking water at levels providing up to 3,000 mg/kg as GAE for up to 17 weeks (Leow *et al.,* 2011, 2013; Sambanthamurthi *et al.,* 2011a,b) or wsPFE by gavage at doses up to 2,000 mg/kg body weight/day for 90 days (Lynch *et al.,* 2017). The safety of the wsPFE ingredient as described herein was assessed in a standard toxicological battery by Lynch *et al.* which included a 90-day oral toxicity study in rats and an assessment of the mutagenicity and genotoxicity of the ingredient in a bacterial reverse mutation test and an *in vitro* chromosome aberration assay. The results of this study served as the pivotal data in assessing the safety of wsPFE. In the 90-day study, the absolute and relative-to-body weights of the uterus were significantly decreased in animals administered 1,000 and 2,000 mg/kg body weight/day; however, no related histopathological findings were reported in these groups. No other treatment-related findings were reported in any other study parameter. Based on the results of this study, a NOAEL of 2,000 mg/kg body weight/day, the highest dose tested, was determined for wsPFE. Considering the estimated intake of wsPFE on a body weight basis in the total population of 59 mg/kg body weight/day, this dose level correlates to a margin of exposure of 34. It is recognized that food ingredients that are comprised primarily of macronutrients are likely to generate margins of safety lower than the standard 100-fold default value following standard toxicological testing due to the potential maximum level of administration coupled to palatability and nutritional imbalances (Renwick *et al.*, 2003). The safety of wsPFE is further supported by the results of the 60-day clinical study (Fairus *et al.,* 2018) and the 30-day clinical study (Hewlings and Kalman, 2020) in which no adverse effects were reported in any study subject consuming up to 450 mg GAE/day. Collectively, the results of the 90-day study in rats and human clinical studies support consumption of wsPFE at the highest estimated conservative levels of intake of 141 mg GAE/person/day (95th percentile in male adults). Considering the production steps to manufacture wsPFE, and the nature of the starting material, it is not expected that the wsPFE final product would pose any allergenicity concerns to consumers. Dietary exposure to various minerals, arsenic, and polyphenols (as GAE) based on the proposed food uses of wsPFE is not expected to pose any safety concerns to final consumers considering they are well below the tolerable upper limits established by EFSA and IOM (in the case of minerals) or well below the background dietary intakes (in the case of polyphenols and arsenic).

6.7 GRAS Panel Evaluation

The MPOB has concluded that wsPFE is GRAS under the conditions of intended use in conventional foods and beverages, as described in Section 1.4, on the basis of scientific procedures. This GRAS conclusion is based on data generally available in the public domain pertaining to the safety of wsPFE, as discussed herein, and on consensus among a panel of experts (the GRAS Panel) who are qualified by scientific training and experience to evaluate the safety of food ingredients. The GRAS Panel consisted of the following qualified scientific experts: Joseph F. Borzelleca (Professor Emeritus, Virginia Commonwealth University School of Medicine), Stanley M. Tarka Jr. (Adjunct Associate Professor, The Pennsylvania State University College of Medicine), and Gary Williams (Professor of Pathology, New York Medical College).

The GRAS Panel, convened by the MPOB, independently and critically evaluated all data and information presented herein, and also concluded that wsPFE is GRAS for use in conventional food products and beverages as described in Section 1.4, based on scientific procedures. A summary of data and information reviewed by the GRAS Panel, and evaluation of such data as it pertains to the proposed GRAS uses of wsPFE is presented in Appendix A.

6.8 Conclusion

Based on the above data and information presented herein, the MPOB has concluded that wsPFE is GRAS, on the basis of scientific procedures, for use in food and beverage products as described in Section 1.4. General recognition of the MPOB's GRAS conclusion is supported by the unanimous consensus rendered by an independent Panel of Experts, qualified by experience and scientific training, to evaluate the use of wsPFE in food and beverages, who similarly concluded that the proposed uses of wsPFE are GRAS on the basis of scientific procedures.

wsPFE therefore may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21, Section 170.3 of the *Code of Federal Regulations*.

Part 7. §170.255 List of Supporting Data and Information

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Part	Section §	Section Title
Subchapter B—Food for Human Consumption		
101—Food labeling	101.12	Reference amounts customarily consumed per eating occasion
170—Food additives	170.3	Definitions
	170.30	Eligibility for classification as generally recognized as safe (GRAS)

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