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Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
United States Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

3/25/2022

RE: GRAS Notification of **Pomella® Pomegranate Extract**
II1083.2-VER.1.3

To Whom It Concerns,

In accordance with **21 CFR Part 170, Subpart E**, we as the agent [REJIMUS, INC., 600 W. Santa Ana Blvd. Ste 1100, Santa Ana, CA 92701], hereby submit the attached GRAS notification on behalf of our client, **Verdure Sciences**, 17150 Metro Park Court, Noblesville, IN 46060, for **Pomella® Pomegranate Extract** intended to be included in dairy products, non-alcoholic beverages, and chocolate candy at levels of 50 mg per serving. The accompanying documentation used in the review is provided in addition to the electronic notification in electronic and CD-ROM version.

Should you have any questions concerning this report, please let me know.

Respectfully,

Jim Lassiter, President/COO
REJIMUS, INC.
jim@rejimus.com

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PART 1 – SIGNED STATEMENTS AND CERTIFICATION

REJIMUS, INC., as Agent for **Verdure Sciences** is hereby submitting a GRAS determination notice in accordance with 21 CFR Part 170, Subpart E.

Name and Address of Notifier and Agent

Agent:
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Tel: +1 (949) 485-2112
www.rejimus.com

Notifier:
Verdure Sciences
17150 Metro Park Court
Noblesville, IN 46060

Name and Address of Manufacturer

Pharmanza Herbal Pvt Ltd
Plot 214, Near Vadalda Patia
Borsad – Tarapur Road
Kanlya, Gujarat
India
FEI: 10031023710

Name of the GRAS Substance

Pomella® Pomegranate Extract

Intended Conditions of Use and Levels of Inclusion

Pomella® Pomegranate Extract is intended for use as an ingredient in dairy products, non-alcoholic juice beverages, and chocolate candy at levels of 50 mg per serving (using the Reference Amount Customarily Consumed – RACC as listed at 21CFR §101.12 Table 2– for the individual food types), not exceeding 1000 mg per day.

Pomella® Pomegranate Extract will not be added to meat and poultry products (including soups and soup mixes containing meat or poultry) and will not be included in foods that are marketed towards infants and young children, inclusive of infant formula. Some of the foods noted for intended use and inclusion have a standard of identity within 21 CFR. Pomella® is not intended for addition to standardized foods unless it is permitted by the applicable standard of identity. The ingredient may be used in products that are similar to foods for which a standard of identity exists. In such cases, the products will not be referred to by their common names.

Basis for GRAS Conclusion

Pursuant to 21CFR §170.30(a) and (b), Pomella® Pomegranate Extract has been concluded to be generally recognized as safe (GRAS) for use as an ingredient in specified foods and beverages as described in this notification, on the basis of scientific procedures.

Premarket Approval Exemption

Verdure Sciences finds that the notified substance, Pomella® Pomegranate Extract, is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on the conclusion that the substance is generally recognized as safe (GRAS) under the conditions of its intended use.

Availability of Information

The data and information that serve as the basis for Verdure's GRAS conclusion are available for review and copying at reasonable times at the offices of the Agent and may also be provided electronically or in hardcopy form.

Should FDA have any questions or additional information requests regarding this notification, the Agent shall provide further clarification and/or further information at:

Attn: Jim Lassiter
REJIMUS, INC.
600 W. Santa Ana Blvd., Suite 1100
Santa Ana, CA 92701
Email: jim@rejimus.com

Trade Secrets

The notification does not contain trade secrets and the data are not exempt from disclosure under the Freedom of Information Act, 5 U.S.C. Part 552.

Certification

Verdure Sciences has concluded that Pomella® Pomegranate Extract is Generally Recognized as Safe for use in dairy products, non-alcoholic juice beverages, and chocolate candy at levels of 50 mg per serving based on scientific procedures in accordance with 21 CFR Part 170, Subpart E. As their Agent, REJIMUS, INC. takes responsibility for all communications on this matter. To the best of our knowledge, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the notified substance.

Name, Position/Title of Responsible Person Who Signs Dossier, and Signature

[redacted]

Jim Lassiter, President/COO
REJIMUS, INC.
jim@rejimus.com

February 28, 2022

PART 2 – IDENTITY, SPECIFICATION, MANUFACTURING AND TECHNICAL EFFECTS

Identification

Botanical Source

The pomegranate is a long-lived vase-shaped densely branched shrub typically trained into a tree growing up to 20 feet with singular or clustered ~1 ¼ inch-wide flowers. Ripening 6 – 7 months after flowering, its nearly round fruit has a prominent calyx and a yellow to red tough leathery rind. The interior is separated by membranous walls containing juicy red arils; within each is a single seed (Morton 1987; USDA-NRCS PLANTS Database).

Taxonomic Lineage

Kingdom: Plantae
Subkingdom: Viridiplantae
Infrakingdom: Streptophyta
Superdivision: Embryophyta
Division: Tracheophyta
Subdivision: Spermatophytina
Class: Magnoliopsida
Superorder: Rosanae
Order: Myrtales
Family: Lythraceae
Genus: *Punica* L.
Species: *P. granatum* L.

Pomegranate Extract

Pomella® Pomegranate Fruit Extract is a dried ethanol extract of the whole fruit of the pomegranate, *Punica granatum* L. (Punicaceae). The extract is a yellowish-brown to brown dry powder, with characteristic odor and flavor. The extract is not intended to be used as a color additive. It is used solely for purposes other than coloring and any color imparted is "clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned" per 21 CFR 70.3(g).

Pomegranate extract is assigned CAS Number [57961-57-9].

Macronutrient Composition

Assays for moisture, ash, fat, and protein were performed on Pomella® for nutritional and compositional information (Table 1). Carbohydrates are calculated by difference.

Table 1. Proximate Analysis of Pomella®

Parameter	Result (%)
Moisture	6.06
Ash	1.75
Fat	0.3
Protein	1.1
Carbohydrates	90.79

Phenolic Characterization

Liu & Seeram (2018) chromatographically analyzed Pomella® Pomegranate Extract and a pomegranate flower extract in determination of their phenolic profiles, tentatively characterizing 71 compounds. The authors stated that pomegranate whole fruit extract should be standardized to characteristic phenolics, specifically naming punicalagins A and B. The punicalagins impart the yellow color to pomegranate husk and are reported to be responsible for the high antioxidant capacity of pomegranate juice (Cerdá et al. 2003a). Commercial pomegranate juice contains about 0.15% punicalagins and 0.25% total phenolics (Gil et al. 2000), mirroring the ratio of these analytes in Pomella® food grade specifications. The profile of Pomella® compared to single strength pomegranate juice is directly applicable with the characterized pomegranate juice with specific notation of the levels of punicalagins. The equivalence in direct terms to pomegranate juice shows that, based on these values, a 50 mg serving of Pomella® is roughly equivalent to 10 mL, or about one third of an ounce, of commercial pomegranate juice with regard to the provision of punicalagins and other polyphenolics. This is the equivalent to 1/24th of the reference amount customarily consumed per eating occasion (RACC) for pomegranate juice as a food product [21 CFR §101.12].

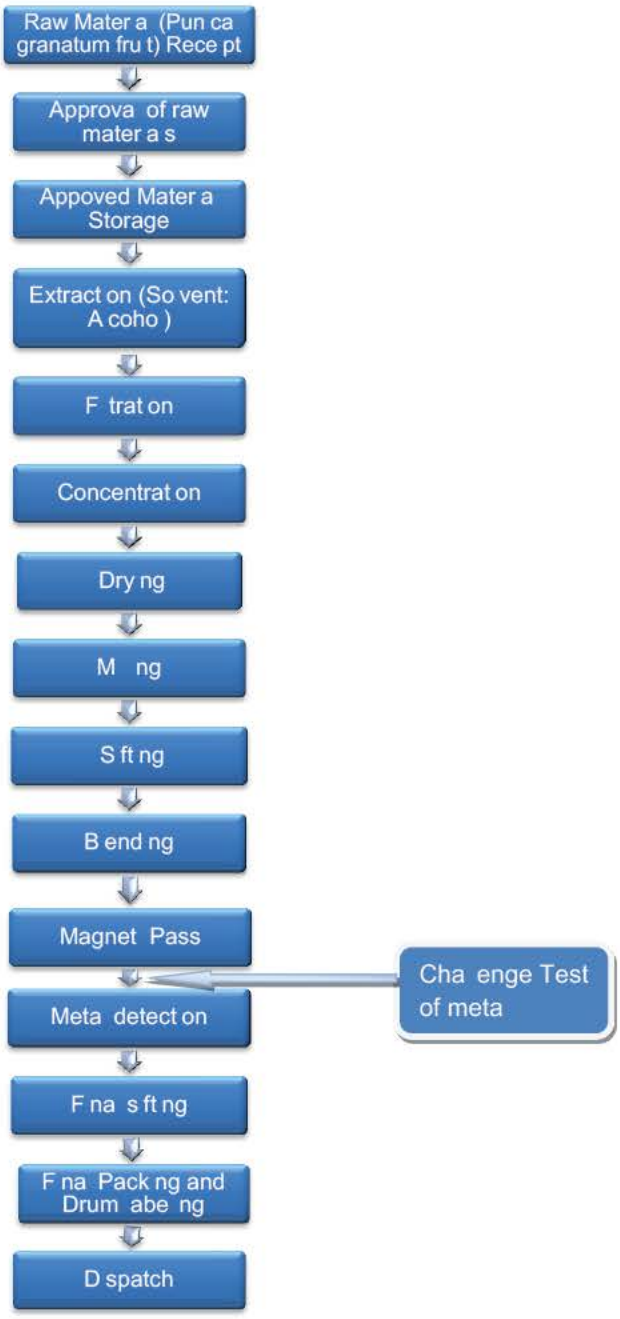
Manufacturing Process

Pomegranate fruit and ethanol are the raw materials employed in the manufacture of Pomella® Pomegranate Extract.

Pomegranate fruit (*Punica granatum* L) is used for the manufacturing of Pomella® products. Pomegranate fruit is received and inspected for macroscopic identification based on physical characteristics and chemical characteristics using thin-layer chromatography. Additionally, the pomegranate fruit is tested for heavy metals and foreign matter and verified that it meets specifications. Approval for release to use for production comes from Quality Control. The fruit is washed with water to remove dust/debris (if any), then it is crushed (using fruit crushing equipment which consists of a charge in-hopper, two crushing rollers, rotating screen, agitating shaft, screw pump and stander).

The crushed mass (including solids & liquids) is used for extraction with 100% ethanol as the extraction vehicle. The extract is then filtered through a cloth filter (Mesh Size: ~400 microns), concentrated by evaporation, and then spray-dried (Inlet Temp: ~160-170 °C & Outlet Temp: 95-100 °C). If required, the dried extract is then milled and sifted through 80 and 100 mesh sieves. Multiple batches of dry extract are blended together to form a single production lot. The process is shown below in Figure 1.

Figure 1. Manufacturing Process Flow Chart



Ingredient Specifications

Food grade specifications for Pomella® Pomegranate Extract have been established by Verdure Sciences. Results from three production batches are presented to demonstrate the ability to consistently produce

the notified substance in conformance with these specifications for physical and chemical attributes, as well as limits on potential contaminants (Table 2).

Table 2. Pomella® Pomegranate Extract food grade ingredient specifications and conforming test results

Parameter	Specifications	Method	Lot LPR1EP-1912J11	Lot LPR1EP-1913K03	Lot LPR1EP-1914K08
Physical					
Identification	Confirms	HPTLC (QC/TEC/078)	Confirms	Confirms	Confirms
Chemical					
Polyphenols	NLT 50.00%	QC/TEC/031	55.08%	57.36%	56.73%
Impurities					
Lead	< 1 ppm	USP <233> ICP-MS	< 0.010 ppm	< 0.010 ppm	< 0.010 ppm
Mercury	< 2 ppm	USP <233> ICP-MS	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm
Arsenic	< 1 ppm	USP <233> ICP-MS	0.014 ppm	0.014 ppm	0.014 ppm
Cadmium	< 1 ppm	USP <233> ICP-MS	< 0.01 ppm	< 0.01 ppm	< 0.01 ppm
Pesticide Residue	USP <561> Screen	USP <561>	Complies	Complies	Complies
Residual Solvents	USP <467> Screen	USP <467>	Complies	Complies	Complies
Microbiological					
Total Plate Count	< 10,000 CFU/g	USP <2021>	< 10 CFU/g	30 CFU/g	< 10 CFU/g
Yeast and Mold	< 1,000 CFU/g	USP <2021>	< 10 CFU/g	10 CFU/g	< 10 CFU/g
Entero-bacteriaceae	< 100 CFU/g	USP <2021>	< 10 CFU/g	< 10 CFU/g	< 10 CFU/g
Coliforms	< 100 CFU/g	USP <2021	< 10 CFU/g	< 10 CFU/g	< 10 CFU/g
Salmonella	Absent/25g	USP <2022>	Absent/25g	Absent/25g	Absent/25g
E. coli	Absent/10g	USP <2022>	Absent/10g	Absent/10g	Absent/10g
S. aureus	Absent/10g	USP <2022>	Absent/10g	Absent/10g	Absent/10g

NOTE: All analytical methods used in the testing against the finished ingredient specifications have been scientifically validated for their respective purposes.

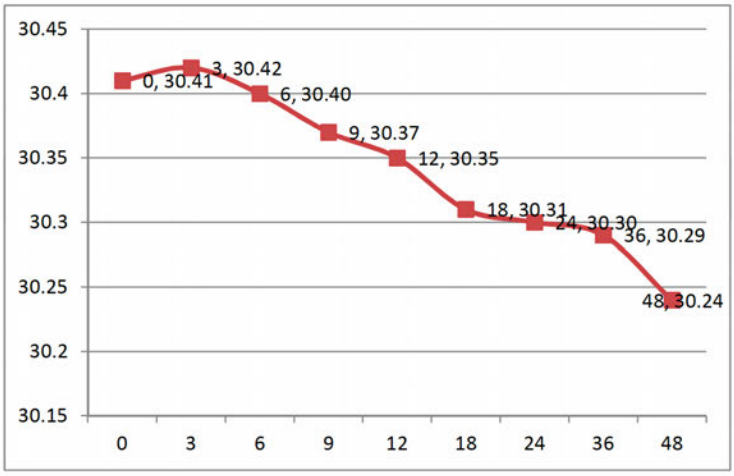
Stability Data

A stability study on Pomella® Pomegranate Extract was conducted under storage conditions of 30°C and a humidity of 65% by Pharmanza Herbal Pvt. Ltd. on behalf of Verdure Sciences.

The data in Figure 2 indicated that Pomella® has a determined shelf life of 48 months from date of manufacture when stored in its original container, away from sunlight and moisture and there is no degradation expected over the indicated shelf life.

Figure 2. Pomella® Pomegranate Extract stability test results for punicalagin A & B content

Months	% Assay (Punicalagin A&B)
0	30.41
3	30.42
6	30.40
9	30.37
12	30.35
18	30.31
24	30.30
36	30.29
48	30.24
Slope	-0.003693127
Intercept	30.40734753



PART 3 – DIETARY EXPOSURE

Intended Use and All Sources in the Diet

Pomella® Pomegranate Extract is intended for use as an ingredient in fluid milk products at a level of 50 mg per serving (using the Reference Amount Customarily Consumed – RACC as listed at 21CFR §101.12 Table 2– for the individual food types), not exceeding 1000 mg per day. To most conservatively estimate the exposure of Pomella® to consumers of foods of the intended inclusion types, cumulative intakes are calculated assuming the extreme example of all servings of consumed food of the described type containing Pomella® at the level notified.

Background Exposure

Pomegranates are fruit native to Iran throughout the Himalayas and have been cultivated since ancient times throughout the Mediterranean regions of Europe, Asia, and Africa. Species have grown in Southern California since it was introduced by the Spanish Missions in 1769. Pomegranates have been consumed worldwide for thousands of years. Existing pomegranate juice beverages available in the market contain anthocyanins (172.2 to 387.4 mg/L), gallagyl-type tannins (67.0 to 1878.8 mg/L), ellagic acid derivatives (26.5 to 243.0 mg/L) and hydrolysable tannins (417.3 to 556.6 mg/L) (Gil et al. 2000). In the U.S., the estimated mean per-user daily intake of pomegranates and pomegranate juice by male and female adults is 110.56 g and 65.76 g, respectively. The estimated 90th percentile per user daily intake of pomegranates and pomegranate juice by male and female adults is 193.19 g and 154.81 g/day, respectively. These intake results were based on food consumption data included in the National Center for Health Statistics (NCHS)'s National Health and Nutrition Examination Surveys (NHANES) (survey data from years 2017 – 2018). It is estimated that the amount of pomegranate juice in products is around 27% due to the astringency of pomegranates. It can therefore be considered that 'pomegranate juice' consumption as recorded by NHANES represents beverages with about 27% pomegranate juice and not the pure juice.

Target consumers' (i.e., adults) consumption of pomegranate and pomegranate juice beverage in the U.S. NHANES (2017 – 2018), presented in Table 3

Table 3. Intakes of Pomegranate and Pomegranate Juice in the US population, estimated using US NHANES 2017-2018 (expressed in g/day)

Population Group	Age Group (Years)	%(n)	Pomegranate and Pomegranate Juice (g/day)	
			Mean (SE)	P90 (SE)
Children	3 to 11	0.2 (2)	9.61 (8.96)	36.24 (14.60)
Female Teenagers	12 to 19	0.67 (3)	26.84 (3.44)	32.60 (1.79)
Male Teenagers	12 to 19	0.22 (1)	40.25 (0.00)	40.25 (0.00)
Female Adults	20 and up	0.46 (10)	65.76 (21.67)	154.81 (61.57)
Male Adults	20 and up	0.61 (12)	110.56 (14.90)	193.19 (43.38)
Total Population	All ages	0.44 (29)	88.42(11.51)	177.20 (32.14)
NHANES = National Health and Nutrition Examination Survey; n = sample size; P90 = 90th percentile; SE = Standard Error				

Background Intake of Polyphenols

Many foods are naturally rich in polyphenols, and there is a long history of safe consumption of polyphenol containing foods (Erdman et al., 2007). An accurate quantification of the dietary intake of polyphenols remains elusive due to the lack of comprehensive food composition databases, despite recent development of polyphenol profiles for certain foods (Erdman et al., 2007). Consequently, a wide range of dietary intake estimates for flavonoids (a family of the polyphenolic compounds mainly found in plants) were reported in peer-reviewed literature (Beecher, 2003, 2004; Prior and Gu, 2005; Erdman et al., 2007). Beecher (2003) estimated the total flavonoids (flavones, flavonols, isoflavones) intake is in the range of 20 to 34 mg/day. Manach et al. (2004) cited the daily intake of flavonols alone as 20 to 35 mg/day. A review by Erdman et al. (2007) suggests that average dietary flavonoid intake in Western populations appears to be in the range of 65 to 250 mg/day, and in the American diet it is about 120 mg/day, with the majority coming from flavan-3-ols. In a recent publication, the average consumption of flavonoids from the diet of male and female U.S. adults was reported to be 207 mg/day (Chun et al., 2010). Bentivegna and Whitney (2002) reported an average consumption of flavonoids from combined natural food sources such as fruits, vegetables, chocolate, and tea, in the range of 460 to 1,000 mg/day which would be equivalent to between 7.7 and 16.7 mg/kg body weight/day for a 60-kg individual. Three major food sources (i.e., tea, legumes, and wines), contributed 45 mg (48%) of total daily PAC intake.

Anthocyanins, a subclass of polyphenols, are present in large amounts in some diets and the potential dietary intake of anthocyanins is among the greatest in the various classes of flavonoids (Wu et al., 2006).

The smallest intake estimate of anthocyanins, 1.3 mg/day for the U.S. population, was reported in a review paper by Erdman et al. (2007). Wu et al. (2006) estimated the daily intake of anthocyanins as 12.5 mg/day based on food consumption data from the NHANES 2001–2002 and levels of anthocyanins present in 24 fruits, vegetables, and nuts foods (CDC, 2007). Servings of 200 g of aubergine or black grapes can provide up to 1,500 mg anthocyanins, and servings of 100 g of berries up to 500 mg. Therefore, an intake of several hundred milligrams would not be considered exceptional (Manach et al., 2004). Since the levels of anthocyanins are consistently similar between various published studies, Wu et al. (2006) attributed the differences between their low estimates as compared to earlier higher estimates to different food intake data that were relied upon to estimate intake of anthocyanins. Based on the high levels of anthocyanins present in fruits and vegetables, intakes of >100 mg/day could be achieved with regular consumption of select fruits or berries, such as blackberries, raspberries, blueberries, or Concord grapes (Wu et al., 2006).

Methods

An assessment of the anticipated intake of Pomella® Pomegranate Extract as an ingredient under the intended conditions of use was conducted using data available in the 2017–2018 cycle of the U.S. NCHS's NHANES.

The NHANES data are collected and released in 2-year cycles with the most recent cycle containing complete data was 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. The NHANES data were employed to assess the mean and 90th percentile intake of Pomella® Pomegranate Extract for each of the following population groups:

- Children 3 to 11
- Teenagers, ages 12 to 19
- Adults, ages 20 and up; and
- Total population (all age and 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 pomegranate and pomegranate juice by the U.S. population. Estimates for the daily intake of pomegranate and pomegranate juice represent projected 2-day averages for everyone 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 to provide representative intakes for the entire U.S. population. "Per capita" intake refers to the estimated intake of pomegranate and pomegranate juice averaged over all individuals surveyed, and therefore includes individuals with "zero" intakes (i.e., those who reported no intake of pomegranate and pomegranate juice during the 2 survey days).

The estimates for the intake of Pomella® Pomegranate Extract were generated using the maximum use-level indicated for the intended food-use, together with food consumption data available from NHANES.

Intake Estimates for Pomella® Pomegranate Extract in proposed dairy milk

The percentage of consumers among all age groups evaluated in the current intake assessment; ranged from 38.21% to 74.04% of the population groups consisted of users of those dairy products in which Pomella® Pomegranate Extract is currently proposed for use (Table 4). Children had the greatest proportion of consumers at 74.04%. 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.

Table 4. Intakes of Dairy Milk in the US population, estimated using US NHANES 2017-2018 (expressed in g/day)

Population Group	Age Group (Years)	% (n)	Dairy Milk (g/day)	
			Mean (SE)	P90 (SE)
Children	3 to 11	74.04 (739)	237.70 (6.65)	456.85 (21.32)
Female Teenagers	12 to 19	42.44 (191)	186.02 (11.53)	362.90 (41.78)
Male Teenagers	12 to 19	54.73 (243)	265.10 (13.96)	477.28 (27.68)
Female Adults	20 and up	38.21 (826)	179.05 (5.05)	360.87 (18.30)
Male Adults	20 and up	44.06 (871)	222.83 (7.12)	499.63 (27.16)
Total Population	All ages	47.61 (3161)	218.16 (3.34)	524.44 (12.19)

NHANES = National Health and Nutrition Examination Survey; n = sample size; P90 = 90th percentile; SE = Standard Error

A summary of the estimated daily intake of Pomella® Pomegranate Extract from the proposed use in dairy milk is provided in Table 5. The calculation is based upon the 50 mg serving multiplied by the cup-equivalent data obtained from the NHANES data in Table 4 above knowing that one cup of milk is equivalent to 244g of fluid dairy milk, based upon the information provided by the Economic Research Service of the USDA in their publication "A Dietary Assessment of the U.S. Food Supply" one serving of dairy is one cup or 244g of any type of fluid milk. The assumption is that every serving of fluid milk is augmented with one serving (50mg) of Pomella® Pomegranate Extract.

Table 5. Summary of the Estimated Daily Intake of Pomella® Pomegranate Extract in Dairy Milk in the U.S. by Population Group (NHANES 2017 - 2018).

Population Group (Years)	Age Group	Per Capita Intake of Dairy Milk (servings/day)		Per Capita Intake of Pomella® (mg/day)	
		Mean	90th Percentile	Mean	90th Percentile
Children	3 to 11	0.97	1.87	48.71	93.62
Female Teenagers	12 to 19	0.76	1.49	38.12	74.36
Male Teenagers	12 to 19	1.09	1.96	54.32	97.80
Female Adult	12 to 19	0.73	1.48	36.69	73.95
Male Adults	20 and up	0.91	2.05	45.66	102.38
Total Population	All ages	0.89	1.85	44.70	92.71

Intake Estimates for Pomella® Pomegranate Extract in proposed juices

The percentage of consumers among all age groups evaluated in the current intake assessment; ranged from 23.59% to 50.20% of the population groups consisted of users of those juice beverage products in which Pomella® Pomegranate Extract is currently proposed for use (Table 6). Children had the greatest proportion of consumers at 50.20%. 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.

Table 6. Intakes of juices in the US population, estimated using US NHANES 2017-2018 (expressed in g/day)

Population Group	Age Group (Years)	% (n)	Juice (g/day)	
			Mean (SE)	P90 (SE)
Children	3 to 11	50.20 (501)	177.96 (7.49)	329.35 (13.30
Female Teenagers	12 to 19	24.22 (109)	172.81 (9.76)	322.95 (7.75)
Male Teenagers	12 to 19	30.18 (134)	245.47 (19.96)	540.02 (26.35)
Female Adults	20 and up	23.59 (510)	175.84 (6.89)	325.50 (24.79)
Male Adults	20 and up	24.23 (479)	216.27 (8.54)	405.03 (39.73)
Total Population	All ages	29.40(1952)	194.06 (3.63)	365.50 (9.54)
NHANES = National Health and Nutrition Examination Survey; n = sample size; P90 = 90th percentile; SE = Standard Error				

A summary of the estimated daily intake of Pomella® Pomegranate Extract from the proposed use in juice is provided in Table 7. The calculation is based upon the 50 mg serving multiplied by "g/day" data obtained from the NHANES data in Table 6 above knowing that one serving of juice is equivalent to 187g, based upon the information provided by the Economic Research Service of the USDA in their publication "A Dietary Assessment of the U.S. Food Supply." One serving of juice is 187g of juice, averaged from the various types of juices listed. The assumption is that every serving of juice is augmented with one serving (50mg) of Pomella® Pomegranate Extract.

Table 7. Summary of the Estimated Daily Intake of Pomella® Pomegranate Extract in juices in the U.S. by Population Group (NHANES 2017 - 2018).

Population Group (Years)	Age Group	Per Capita Intake of Juice (servings/day)		Per Capita Intake of Pomella® (mg/day)	
		Mean	90th Percentile	Mean	90th Percentile
Children	3 to 11	0.95	1.76	47.58	88.06
Female Teenagers	12 to 19	0.92	1.73	46.21	86.35
Male Teenagers	12 to 19	1.31	2.89	65.63	144.39
Female Adult	20 and up	0.94	1.74	47.02	87.03
Male Adults	20 and up	1.16	2.17	57.83	108.30
Total Population	All ages	1.04	1.95	51.89	97.73

Intake Estimates for Pomella® Pomegranate Extract in proposed chocolate candies

The percentage of consumers among all age groups evaluated in the current intake assessment; ranged from 5.76% to 19.54% of the population groups consisted of users of those products in which Pomella® Pomegranate Extract is currently proposed for use (Table 8). Female adults had the greatest proportion of consumers at 19.84%. 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.

Table 8. Intakes of chocolate candies in the US population, estimated using US NHANES 2017-2018 (expressed in g/day).

Population Group	Age Group (Years)	% (n)	Chocolate candies (g/day)	
			Mean (SE)	P90 (SE)
Infants and Young Children	0 to 2	5.76 (35)	8.48 (1.08)	19.54 (2.64
Children	3 to 11	19.54 (195)	15.87 (1.26)	41.83 (4.96)
Female Teenagers	12 to 19	15.78 (71)	19.95 (2.11)	34.42 (5.35)
Male Teenagers	12 to 19	13.74 (61)	24.86 (3.25)	58.93 (12.07)
Female Adults	20 and up	19.84 (429)	20.99 (0.95)	47.09 (3.73)
Male Adults	20 and up	15.53 (307)	24.74 (1.46)	59.90 (5.05)
Total Population	All ages	16.54 (1098)	21.54 (0.64)	47.50 (2.90)
NHANES = National Health and Nutrition Examination Survey; n = sample size; P90 = 90th percentile; SE = Standard Error				

A summary of the estimated daily intake of Pomella® Pomegranate Extract from the proposed use in chocolate candies is provided in Table 9. The calculation is based upon the 50 mg serving multiplied by the serving data obtained from the NHANES data in Table 8 above knowing that one serving of chocolate is equivalent to 30g, based upon the "reference amounts customarily consumed (RACCs)." The assumption is that every serving of chocolate candy is augmented with one serving (50mg) of Pomella® Pomegranate Extract.

Table 9. Summary of the Estimated Daily Intake of Pomella® Pomegranate Extract in chocolate candies in the U.S. by Population Group (NHANES 2017 - 2018)

Population Group (Years)	Age Group	Per Capita Intake of chocolate candies (servings/day)		Per Capita Intake of Pomella® (mg/day)	
		Mean	90th Percentile	Mean	90th Percentile
Children	3 to 11	0.53	1.39	26.45	69.72
Female Teenagers	12 to 19	0.67	1.15	33.25	57.37
Male Teenagers	12 to 19	0.83	1.96	41.43	98.22
Female Adult	20 and up	0.70	1.57	34.98	78.48
Male Adults	20 and up	0.82	2.00	41.23	99.83
Total Population	All ages	0.72	1.58	35.90	79.17

Results of Intake Estimates for Polyphenols

Among the individual population groups, male teenagers were determined to have the greatest mean at 65.63 mg potential consumption through juices, while female teenagers at 57.37 mg were determined to have the smallest 90th percentile intakes of polyphenols from Pomella® Pomegranate Extract through consumption of chocolate candies. Infants are not the expected consumer group for Pomella® Pomegranate Extract and thus were not taken into consideration.

Table 10. Summary of the Estimated Daily Intake of Pomella® Pomegranate Extract from Proposed Food-Use in the U.S. by Population Group (mg)

Population Group (Years)	Age Group	Pomegranate & Pomegranate Juice		Dairy Milk		Juices		Chocolate Candies	
		Mean	90th %	Mean	90th %	Mean	90th %	Mean	90th %
Children	3 to 11	9.61	36.24	48.71	93.62	47.58	88.06	26.45	69.72
Female Teenagers	12 to 19	26.84	32.60	38.12	74.36	46.21	86.35	33.25	57.37
Male Teenagers	12 to 19	40.25	40.25	54.32	97.80	65.63	144.39	41.43	98.22
Female Adult	20 and up	65.76	154.81	36.69	73.95	47.02	87.03	34.98	78.48
Male Adults	20 and up	110.56	193.19	45.66	102.38	57.83	108.30	41.23	99.83
Total Population	All ages	88.42	177.20	44.70	92.71	51.89	97.73	35.90	79.17

Summary and Conclusions

Consumption data and information pertaining to the intended food-use of Pomella® Pomegranate Extract were used to estimate the per capita and consumer-only intakes of this ingredient for 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 Pomella® Pomegranate Extract at the 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 Pomella® Pomegranate Extract will have 100% market penetration in the identified food category.

Cumulative Intake

In determination of the greatest level of Pomella® Pomegranate Extract potentially consumed by ingestion of the indicated food types, extreme assumptions are made:

Pomella® is included in every serving of food of the types potentially containing the ingredient.

The average consumer of each type of Pomella®-containing food is a consumer of all categories of fluid milk product with Pomella®.

The average consumer of each type of Pomella®-containing food is a consumer of all categories of juices with Pomella®.

The average consumer of each type of Pomella®-containing food is a consumer of all categories of chocolate candy products with Pomella®.

Based on the presented data and assumptions and using the high-level extrapolated consumption scenarios discussed above, the cumulative maximum estimated intake of Pomella® based on the 90th percentile is 310.51 mg per day for male adults ages 20 years and older an increase of 117.32 mg per day over the current estimated polyphenol intake.

This amount of Pomella® is equivalent to 2-3 fl oz of commercial pomegranate juice based on the phenolic profile. A serving of pomegranate juice is 8 fl oz based on Reference Amounts Customarily Consumed (RACC) per eating occasion [21 CFR §101.12]. Thus, a day's consumption of foods containing Pomella® at the intended levels (50 mg/serving) corresponds to less than half the RACC pomegranate juice per day.

Substances Naturally Present or Due to Manufacturing

Being a source of punicalagins and polyphenols in general, ingestion of foods containing Pomella® Pomegranate Extract results in an additive intake of these compounds to the regular diet. It is difficult to estimate the average daily intake of polyphenols for reasons including lack of standardized analytical methods to detect and measure these thousands of compounds having great structural diversity, variation in their concentration in a particular food, and interindividual variation in metabolism. Vegetables, legumes, and cereals provide polyphenols, but the major sources in the diet are fruit and beverages such as coffee, tea, and red wine. Avoidance of polyphenols in the diet is challenging, and intake of foods and beverages high in these compounds adds to the difficulty in accurately estimating consumption values

due to the variance inherent to individual food type selection (Manach et al. 2004, Scalbert & Williamson 2000).

An average polyphenol intake of roughly 1 g per day in the United States was originally determined in 1976, and this value has since been confirmed by Scalbert & Williamson (2000) in their evaluation of dietary intake and bioavailability of polyphenols. Moreover, the authors state that a person consuming different servings of foods or beverages high in polyphenols in a day would effectively guarantee ingestion of greater than 1 gram of polyphenols.

Published in 2015, a study by Zamora-Ros et al. estimated dietary intake of polyphenols among various demographics within selected European countries utilizing self-reported 24-hour dietary recall data in conjunction with the Phenol-Explorer database. Mean total daily polyphenol intake was found to range from a low in Greece of 744 mg and 584 mg for men and women, respectively, to a high of 1,786 mg for men and 1,626 mg for women in Aarhus, Denmark. Saura-Calixto et al. (2007) state an even greater estimation in the Spanish diet of between 2,590 to 3,016 mg per person per day.

For examples of how particular food selections affect polyphenol intake levels on a per serving basis, Table 11 presents estimated polyphenol intake based on concentrations determined by Péréz-Jiménez et al. (2010) using the Phenol-Explorer database (www.phenol-explorer.eu) or measured by Gil et al (2000) in commercial pomegranate juice. Serving sizes were applied using either the Reference Amounts Customarily Consumed (RACC) presented at 21 CFR 101.12(b) or TTB Ruling 2013-2 for alcoholic beverages.

Table 11. Polyphenol content per serving of selected foods and beverages

Food	Polyphenol Content	Serving Size	Polyphenols / Serving
Cloves	15.188 %	0.5 g	76 mg
Cocoa Powder	3.448 %	5 g	172 mg
Dark Chocolate	1.664 %	30 g	499 mg
Blueberries	0.836 %	50 g	418 mg
Plums	0.377 %	140 g	528 mg
Nectarines	0.025 %	140 g	35 mg
Coffee	0.214 %	360 ml	770 mg
Black Tea	0.102 %	360 ml	367 mg
Green Tea	0.089 %	360 ml	320 mg
Pomegranate Juice	0.257%	240 ml	617 mg
Red Wine	0.101 %	5 fl oz	150 mg
White Wine	0.010%	5 fl oz	15 mg

The estimated high daily intake of 310.51 mg of Pomella® corresponds to an estimated total polyphenol content of 274.82 mg based on the ingredient's specifications. Variation in potential polyphenol intake

based on individual food item selection, as shown in Table 11, is much greater than the level of polyphenols borne in the high-level estimate of Pomella®-containing foods. From this estimation, a serving of dark chocolate delivers nearly 2½ times the quantity of total polyphenols compared to the high-level estimate of cumulative daily Pomella® intake; a serving of coffee provides almost 4 times the amount. Total daily polyphenol intake is predominantly dependent on individual food choices rather than consumption of intended amounts of Pomella®, even for consumers of all food types assumed to contain the ingredient.

Since Pomella® is extracted with alcohol (ethanol), residual amounts are tested for each batch by USP <467> to ensure sufficient drying and verify solvent supply.

No reaction products are expected to form in foods in which Pomella® is formulated.

PART 4 – SELF-LIMITING LEVELS OF USE

The sensory properties of Pomella® limit the levels feasibly formulated in foods due to its earthy flavor and moderate astringency. The content of epigallocatechin creates the astringency, and astringency can result in a dry, grainy, course taste according to Vidal et. al. (2003).

PART 5 – EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958

As the conclusion of general recognition of safety is through scientific procedures, this Part is not applicable. Information concerning the historical use of the source botanical in the food supply and the qualitative and quantitative equivalencies between pomegranate and Pomella® are discussed as part of the scientific procedures upon which the general recognition of safety is based.

PART 6 – NARRATIVE

Introduction

The pomegranate is native to the area from modern-day Iran to Nepal, and its cultivation spread throughout the region surrounding the Mediterranean in ancient times owing to its use as a food and source of juice. Extending to Southern India by the first century, pomegranate also spread to other important growing areas such as China, Saudi Arabia, and the Americas (Morton 1987). Brought by Spanish missionaries along with other important fruit-bearing plants, pomegranate's introduction to the New World predates the establishment of the United States, and its commercial production began in 1896 (LaRue 1980, UC Davis 2020).

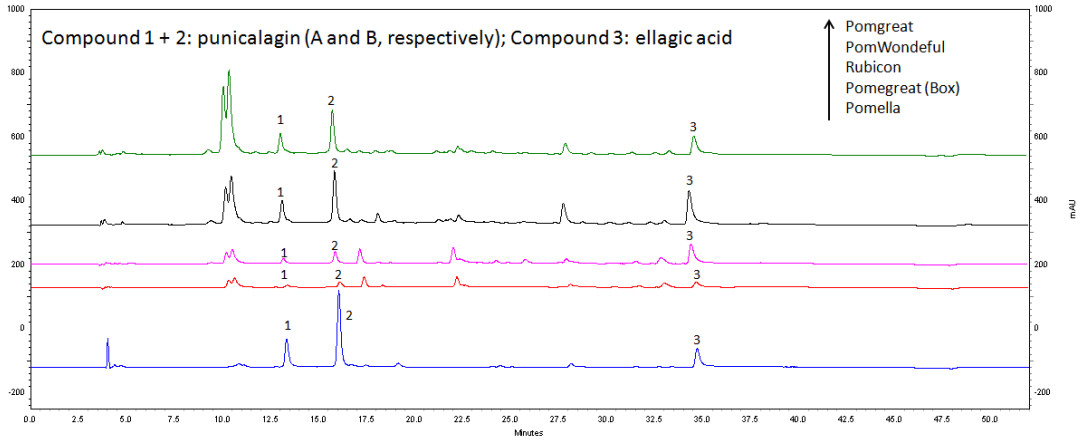
Relation Between Commercial Pomegranate Juice and Pomella®

- Commercial pomegranate juice contains 0.25% total polyphenols and 0.15% punicalagins (Gil et al. 2000).
- Pomella® Pomegranate Extract contains ≥ 50% total polyphenols and ≥ 30% punicalagins.

Based on the above, commercial pomegranate juice and Pomella® contain the same ratio of punicalagins to total polyphenols, owing to their common source (whole pomegranate fruit without chemical alteration). At the determined 0.15% concentration of punicalagins, a single 8 oz serving (RACC) of pomegranate juice contains about 360 mg of these pomegranate marker compounds, which is equivalent to 24 servings of Pomella® containing foods, or roughly 3 times the high-level consumption estimation for Pomella® identified in this report. A single serving of a Pomella® containing food is equivalent to 2-3 fl oz of pomegranate juice based on these phenolic markers, which is less than half the RACC for pomegranate juice.

The following Figure 3 depicts the similarities in the chromatographic profiles of Pomella® with other pomegranate extract containing products that are already on the market:

Figure 3. Pomella® vs. Commercial Juices Punicalagin and Ellagic Acid Content (Data obtained from Verdure Sciences)



Metabolism of Pomella®

The marker compound and main phenolic component of Pomella®, punicalagins A and B, are ellagitannins. Ellagitannins are known to be hydrolyzed in the gut to ellagic acid which is then metabolized by intestinal microbiota to produce urolithins (Ludwig et al. 2015, Landete 2011, Espín et al. 2007, Mertens-Talcott et al. 2006).

To evaluate possible toxic effect of punicalagins, an *in vivo* study was conducted by Cerdá et al. (2003b) by providing either commercial feed or commercial feed supplemented to contain 6% punicalagin from pomegranate husk extract to 10 female rats divided into 2 groups of 5 for 37 days. Some measures of food intake and growth rate were lower in rats given punicalagin during the first 15 days, but without significant adverse events, which could be explained by the lower nutritional value or palatability of the test feed containing 20% pomegranate husk extract. During the third week however, feed intake was greater than in the control group. The mean oral consumption of punicalagin was determined to be 0.9 g/day (~4.8 g/kg body weight), the equivalent of a 60 kg person consuming about 19,200 servings Pomella®.

A study was conducted by Mertens-Talcott et al. (2006) to determine the absorption and antioxidant effects of pomegranate extract using 800 mg of Pomella® as the test article. Each daily serving of Pomella® used for the study contained 330.4 mg of punicalagins A&B and 21.6 mg of ellagic acid, as measured by HPLC analysis. After a 3-day washout period, 11 male and female subjects received 2 capsules, each containing 400 mg of Pomella®, with 6 oz of water. Blood was drawn at baseline, 30 minutes after, and at hours 1, 2, 4, 6, 8, and 24 post-ingestion. To control additional intake of polyphenols, subjects were given crackers and water 2-3 hours after ingestion, a polyphenol-free low-fat sandwich 4-5 hours after consumption, and a frozen polyphenol-free pasta dinner to take home. Ellagic acid as well as the ellagic acid-derived metabolites urolithin A, hydroxyurolithin A, urolithin A-glucuronide, urolithin B, and dimethyl ellagic acid glucuronide were detected in subjects' blood samples by HPLC-MS; Figure 4 below shows plasma concentrations of ellagic acid over time while Figure 5 below shows chromatograms obtained for individual metabolites' peaks. Results show high variability between subjects in detected metabolites, with noncompliance assumed in the case of three individuals' extraordinarily high levels of plasma concentrations of ellagic acid after 24 hours.

Figure 4. Plasma concentrations of ellagic acid after the consumption of 800 mg Pomella®

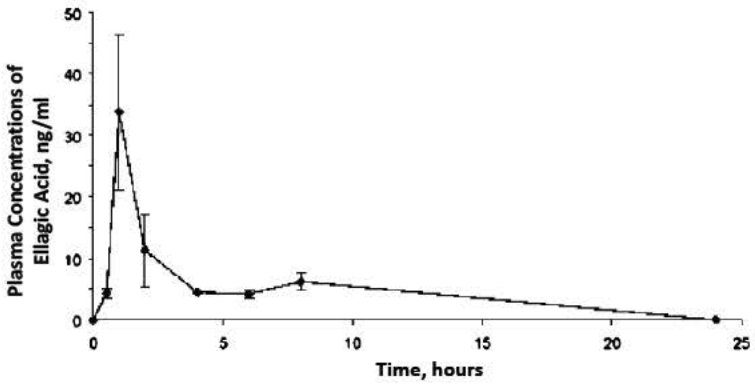


Figure 5. LC-MS extracted ion chromatograms showing the presence of ellagitannin metabolites in human plasma. (A) ellagic acid, (B) urolithin A, (C) hydroxyurolithin A, (D) urolithin B, (E) urolithin A-glucuronide, (F) dimethyl ellagic acid glucuronide.

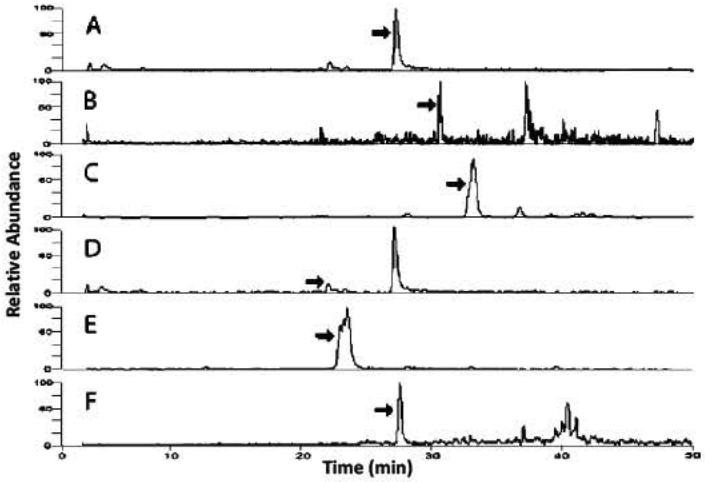
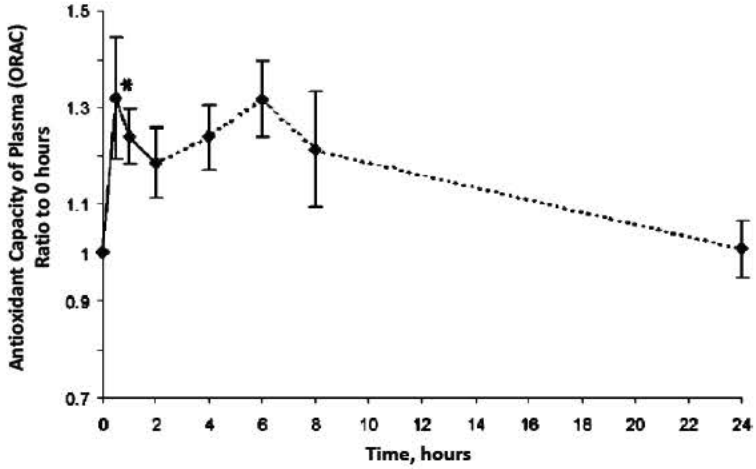


Figure 6. Antioxidant capacity in plasma after the consumption of 800 mg of Pomella®. Values significantly different ($p \leq 0.05$) from baseline are marked with an asterisk.



Antioxidant capacity (ORAC assay) in plasma was significantly increased after 30 minutes with a second peak in capacity seen after 6 hours as presented in Figure 6.

CF-DA assay was additionally performed to determine a potential decrease in the generation of reactive oxygen species (ROS). No change was seen in the generation of ROS.

Plasma concentrations of interleukin-6 were also measured to determine the effects of Pomella® on a marker of immune health; levels were not significantly increased after 4 hours. Increases seen after 6 and 8 hours could not be determined to be fully attributable to the pomegranate extract due to the ingestion of food after 4-5 hours. No adverse events are reported (Mertens-Talcott et al. 2006).

Consumption of polyphenols in the ordinary diet is haphazard owing to the prevalence of these compounds in limited areas of food intake as shown. The polyphenols included in Pomella® Pomegranate Extract mirror those of pomegranate juice. These compounds are classified as ellagitannins which hold a specific chemical classification within the realm of polyphenols. Notations in the literature relating to potentially negative aspects of the consumption of polyphenols focus on flavones and flavone glycosides and other classes of polyphenols. These demonstrated challenges are from the consumption of polyphenols other than those found in Pomella® Pomegranate Extract. Data and information concerning the potential for these negative effects are relevant only to those specific compounds. Studies of the safety of polyphenols reflects concerns and finding for a variety of those compounds such as quercetin, epigallocatechin gallate (EGCG) and the anthocyanin cyanidin-3-clycodise (C3G) demonstrated a range of potentially neurotoxic effects (Silva and Pogacnik, 2020). Additional findings in the literature include a more specific detailed compositional makeup of the polyphenols in pomegranate (Li et.al., 2016). The constituents determined did not include the polyphenols of concern as shown in in the literature.

Toxicity Studies

Acute Toxicity Studies

Studies designed to determine oral LD_{50} of Pomella® Pomegranate Extract in male and female Wistar rats (6/sex/group) and Swiss albino mice (6/sex/group) were conducted by Patel et al. (2008). Doses of either 0, 50, 500, or 5,000 mg/kg body weight were administered by gavage. All animals were observed for 14 days for any signs of morbidity or mortality. Pathological examinations were undertaken on Day 15. No mortalities occurred during the 14-day post-administration period, and necropsy at the end of the study did not reveal any gross pathological abnormalities. The oral LD_{50} in Wistar rats and Swiss albino mice was determined to be greater than 5,000 mg/kg body weight. The established No Observed Adverse Effect Level (NOAEL) of 5,000 mg/kg body weight, when employing a safety factor of 1/100 in application of animal data, corresponds to a safe level in humans of 50 mg/kg body weight, or 3,000 mg for a 60 kg person.

Studies designed to determine intraperitoneal LD_{50} of Pomella® in male and female Wistar rats and Swiss albino mice were conducted by Patel et al. (2008) as well. Doses of either 0, 100, 200, or 300 mg/kg body weight/day were administered to the rats while doses of either 0, 100, 150, or 200 mg/kg body weight/day were used in the mouse model. All animals were observed for 14 days for any signs of morbidity or mortality. Pathological examinations were undertaken on Day 15. Intraperitoneal LD_{50} was determined to be 217.5 mg/kg in Wistar rats and 187.5 mg/kg in Swiss albino mice.

Subchronic Toxicity Study

Wistar rats (10/sex/group) were administered orally by gavage either 0, 60, 240, or 600 mg/kg body weight Pomella® Pomegranate Extract in a 90-day oral toxicity study conducted by Patel et al. (2008). Two additional groups of 10 Wistar rats/sex/group were given either 0 or 600 mg/kg body weight/day for 90 days followed by no additional treatment for 28 days. All animals in each of the 6 groups survived until

scheduled necropsy. Statistical analysis of feed and water consumption, urinalysis, hematology, serum chemistry, organ weights, and macroscopic and microscopic examinations showed no treatment-related statistically significant differences between placebo and treatment groups. The NOAEL seen in this study of 600 mg/kg body weight corresponds to 6 mg/kg in humans, or 360 mg in a 60 kg person.

Human Studies

Study 1

One hundred men and women between the ages of 40 and 60 with myocardial infarction were divided into treatment and placebo groups of 50 patients each in a double-blind trial by Goyal et al. (2016a). Treatment group consumed tablets containing 300 mg whole fruit pomegranate extract from Pharmanza (the manufacturer of Pomella®) twice per day for 15 days while the other group received matching placebo. The extract was produced by the same process as the notified substance, except using aqueous ethanol (as opposed to absolute ethanol) as the extraction solvent, resulting in a concentration of only 14.51% punicalagins. Treatment was in addition to existing pharmaceutical protocol. At the end of the first 15-day period, all patients were recalled for clinical evaluation, compliance and adverse effect monitoring, and tablet refill for the following 15 days. Evaluations and observations were repeated at the end of the month-long treatment period. Improvements were seen in serum measurements of triglycerides, total cholesterol, HDL, LDL, Non-HDL cholesterol, OX-LDL, and homocysteine. Adverse events were not reported in any patients, taking up to 600 mg per day of whole fruit pomegranate extract from Pharmanza, equivalent to roughly 300 mg per day of the notified substance, Pomella® Pomegranate Extract (30% punicalagins).

Study 2

Forty men and women between the ages of 40 and 55 with diabetes mellitus type 2 and myocardial infarction were divided into 2 groups of 20 patients each in a double-blind trial by Goyal et al. (2016b). One group was instructed to ingest tablets containing 300 mg whole fruit pomegranate extract from Pharmanza twice per day and the other was to consume matching placebo. Treatment was in addition to existing pharmaceutical protocol. With reduced levels of fasting blood glucose and increased measurements of serum antioxidant activity, significant improvements in observed parameters indicate improved prognosis in the treatment group. Adverse events were not reported in any patients, taking up to 600 mg per day of whole fruit pomegranate extract from Pharmanza, equivalent to roughly 300 mg per day of the notified substance, Pomella® Pomegranate Extract (30% punicalagins).

Study 3

A study completed by Tanner et al (2020) utilized 8 individuals who were training for half marathon race. The eight subjects were given pomegranate extract in a study to determine whether pomegranate extract in combination with curcumin could reduce inflammation and swelling during training. The regimen started 26 days prior to the marathon and participants were provided the supplements containing approximately 30% punicalagins in 500mg of pomegranate extract. None of the participants dropped out of the study due to the treatment, and all of the participants experienced no adverse effects from the pomegranate extract.

Study 4

DiSilvestro et al. (2009) devised a study to evaluate changes in measurements of parameters associated with oral hygiene. 16 men and 16 women were recruited for the 4-week study which divided them into 2 groups of 8 men and 8 women, with one group receiving 100 mg per day of Pomella® and the other receiving an equal amount of corn muffin mix (used as placebo). The 100 mg daily amount was divided into 3 equal portions, and each dissolved in 35 ml water to be used as a mouth rinse, for 1 minute thrice daily. Rinsing with Pomella® was shown to reduce total protein content, as well as aspartate aminotransferase and alpha-glucosidase activity, while increasing ceruloplasmin activity levels. No adverse effects were reported by any of the subjects.

Related Studies

A systematic literature search and review dealing with the safety of pomegranate products carried out by Vlachojannis et al. (2015) concluded that pomegranate products can safely be used in high doses. Moreover, the authors state that commercial pomegranate products vary greatly in their content of measured constituent compounds, highlighting that many factors affect pomegranate end products and suggesting regulatory guidance and control be incorporated in declaration of HPLC-analyzed polyphenols and photometrically analyzed phenolics in general.

Conclusion

The scientific data, information, methods, and principles described in this notice provide the basis for conclusion that Pomella® Pomegranate Extract is generally recognized among qualified experts to be safe for inclusion in the food types described in the amounts noted. The historic and current consumption of the source botanical, pomegranate, and the juice from the fruit in the food supply serves as the foundation on which the safety of this substance is established. The scientific determinations of the safety of the substance present data regarding the safety of the specific pomegranate whole fruit extract, Pomella®, as identified and described in this notice.

Punicalagins A & B, ellagitannins identified as appropriate marker compounds for identification of pomegranate, are polyphenols of known metabolism in humans. Metabolism of the specific pomegranate preparation Pomella® Pomegranate Extract has been shown in humans upon ingestion of 800 mg, or 16 servings, of Pomella®. Toxicity studies performed specifically on the unique pomegranate marker polyphenols, punicalagins A & B, showed no significant adverse events in rats ingesting an average of 0.9 grams per day, or ~4.8 g/kg body weight, the equivalent of a 60 kg human consuming 19,200 servings of Pomella®-containing foods per day.

The notified pomegranate extract has an additive effect to total polyphenol exposure in the diet, which has historically been difficult to estimate. Day-to-day selection of certain common foods such as chocolate, fruit, tea, and wine, consumed in customarily consumed quantities, holds much greater weight when estimating exposure to total polyphenols than does selection of foods containing Pomella®. The same holds true for the marker polyphenols themselves, punicalagins A & B, for which the historical, current, and widespread consumption of pomegranate juice, in amounts customarily consumed, results in levels of exposure several times greater than ingestion of Pomella®-containing foods. Americans drink an average of 0.35 servings, or 2.8 fl oz, of juice per day. Even if all such juice consumed were pomegranate juice, the average normal intake would be the equivalent of over 8 servings of Pomella® per day, which is

also greater than the high-level estimated daily intake of Pomella®. As a serving of Pomella® is roughly equivalent to about 1/3 fl oz of pomegranate juice, drinking a full 8 fl oz serving corresponds to about 24 servings of Pomella®-containing foods. This is greater than 3 times the high-level estimated daily intake of Pomella®.

Toxicity studies performed specifically on Pomella® support the recognized safety of ingestion of the intended amounts of the notified pomegranate extract in the described food types. Data from the acute and subchronic animal toxicity studies correspond to NOAELs of 50 mg/kg body weight and 6 mg/kg body weight, respectively, using a safety factor of 1/100. Efficacy studies presented no adverse effects in humans taking up to 600 mg Pomella® per day.

All data and information pertaining to the studies performed on the material were made available to the Expert Panel, and their findings reflect review of the totality of the information used in the preparation of this notice as shown on the Expert Panel Endorsement pages.

PART 7 – SUPPORTING DATA AND INFORMATION

Generally Unavailable

N/A

Generally Available

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Expert Panel Endorsement

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Verdure Sciences Pomella® Pomegranate Extract

March 18, 2021

Verdure Sciences intends to market ***Pomella® Pomegranate Extract*** which is a dried ethanol extract of the whole fruit of the pomegranate, *Punica granatum* L. Pomella® Pomegranate Extract is intended to be included in dairy products, non-alcoholic beverages, and candy at levels of 50 mg per serving not to exceed 1000 mg/day.

The application of the ***Pomella® Pomegranate Extract*** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Verdure Sciences, a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended use of ***Pomella® Pomegranate Extract*** as an ingredient in dairy products, non-alcoholic beverages, and candy is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Louis Ndife, Ph.D. (Expert Engine International Group of Consultants), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Verdure Sciences. ***Pomella® Pomegranate Extract***, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy product, non-alcoholic beverage, and candy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products, non-alcoholic beverages, and candy products that include Verdure Sciences' ***Pomella® Pomegranate Extract*** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good Manufacturing

Practice (cGMP), are safe for human consumption. These determinations are made based on support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY JEAN MOLDENHAUER, M. SC.

I, Jeanne Moldenhauer, hereby affirm that ***Pomella® Pomegranate Extract*** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature [redacted] Date: 3/18/21

Jeanne Moldenhauer
Excellent Pharma Consulting

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Verdure Sciences Pomella®, a Pomegranate Fresh Fruit Dry Extract

April 2, 2021

Verdure Sciences intends to market ***Pomella®*** which is an ethanol dry extract of the whole fresh fruit of the pomegranate, *Punica granatum* L. ***Pomella®*** is intended to be included in dairy products, non-alcoholic beverages, and candy at levels of 50 mg per serving not to exceed 1000 mg/day.

The application of the ***Pomella®*** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Verdure Sciences, a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Pomella®*** as an ingredient in dairy products, non-alcoholic beverages, and candy is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Louis Ndife, Ph.D. (Expert Engine International Group of Consultants), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Verdure Sciences. ***Pomella®***, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy product, non-alcoholic beverage, and candy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products, non-alcoholic beverages, and candy products that include Verdure Sciences' ***Pomella®*** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY STEVEN DENTALI, PH.D.

I, Steven Dentali, hereby affirm that ***Pomella®, a Pomegranate Fresh Fruit Dry Extract*** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature:_ [redacted] _ Date:_____

Steven Dentali, Ph.D.
Dentali Botanical Sciences

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Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Verdure Sciences Pomella® Pomegranate Extract

March 18, 2021

Verdure Sciences intends to market ***Pomella® Pomegranate Extract*** which is a dried ethanol extract of the whole fruit of the pomegranate, *Punica granatum* L. Pomella® Pomegranate Extract is intended to be included in dairy products, non-alcoholic beverages, and candy at levels of 50 mg per serving not to exceed 1000 mg/day.

The application of the ***Pomella® Pomegranate Extract*** identified in this dossier is further demonstrated in this submission as Generally Recognized as Safe through support from the application of scientific procedures evaluating the safety of the item.

At the request of Verdure Sciences, a panel of independent scientists (the "Expert Panel"), qualified by their relevant national experience, education and training, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of ***Pomella® Pomegranate Extract*** as an ingredient in dairy products, non-alcoholic beverages, and candy is safe, suitable, and would be Generally Recognized as Safe (GRAS) based on a combination of historic use and scientific procedures. The Expert Panel consisted of following experts: Steven Dentali, Ph.D. (Dentali Botanical Sciences), Louis Ndife, Ph.D. (Expert Engine International Group of Consultants), and Ms. Jeanne Moldenhauer, M.Sc. (Excellent Pharma Consulting).

The Expert Panel, independently and collectively, evaluated the dossier inclusive of the following:

Basis for GRAS Determination	Narrative Summary
Claim Regarding GRAS Status	Determination of the Expert Panel
Manufacturing Process	Summary and Diagrams
Stability Data	Data and Presentation
Dietary Exposure	Summary of intended exposure
Basis for Determination	Discussion of studies
Public and Private Studies	Supporting studies included

In addition, the Expert Panel evaluated all other information deemed necessary and/or sufficient in order to arrive at its independent, critical evaluation of these data and information. The Expert Panel has attained a unanimous conclusion that the intended uses described herein for Verdure Sciences.

Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Determination of Verdure Sciences Pomella® Pomegranate Extract

Pomella® Pomegranate Extract, meeting appropriate food-grade specifications as described in the supporting dossier, as a dairy product, non-alcoholic beverage, and candy ingredient is identified as Generally Recognized as Safe (GRAS) by Self-determination for use as a food ingredient across a range of food categories identified in the dossier. Such dairy products, non-alcoholic beverages, and candy products that include Verdure Sciences' ***Pomella® Pomegranate Extract*** in accordance with the described applications and levels specified in the dossier, manufactured according to current Good Manufacturing Practice (cGMP), are safe for human consumption. These determinations are made based on support from scientific procedures.

The individual endorsement pages follow hereunder.

ENDORSEMENT BY LOUIS NDIFE, PH.D.

I, Louis Ndife, hereby affirm that ***Pomella® Pomegranate Extract*** is Generally Recognized as Safe by Self-determination based upon my review and participation in the appointed Expert Panel.

Signature: louis ndife [redacted] Date: march 18, 2021

Louis Ndife, Ph.D.

Expert Engine International Group of Consultants

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