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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

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].

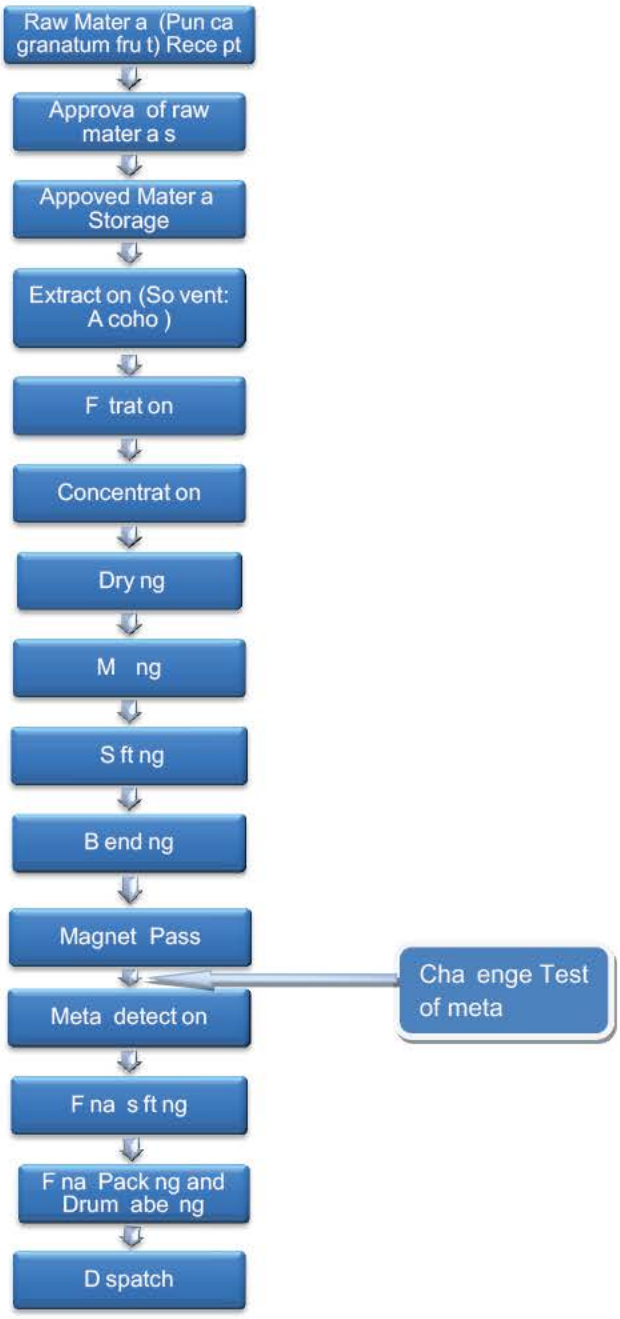
Manufacturing Process

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.

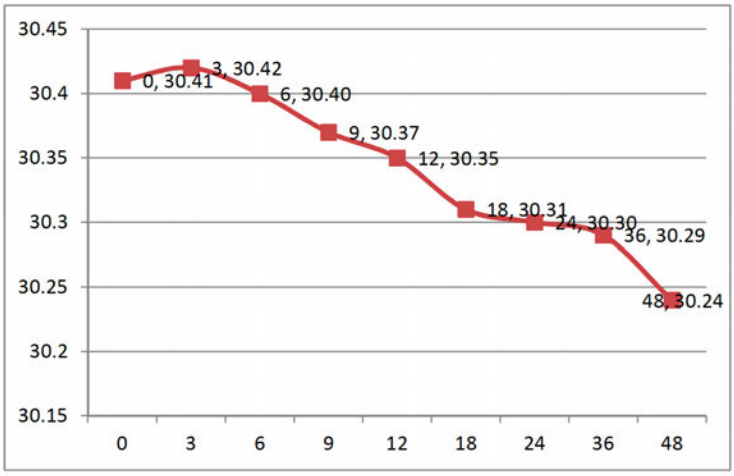
Stability Data

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).

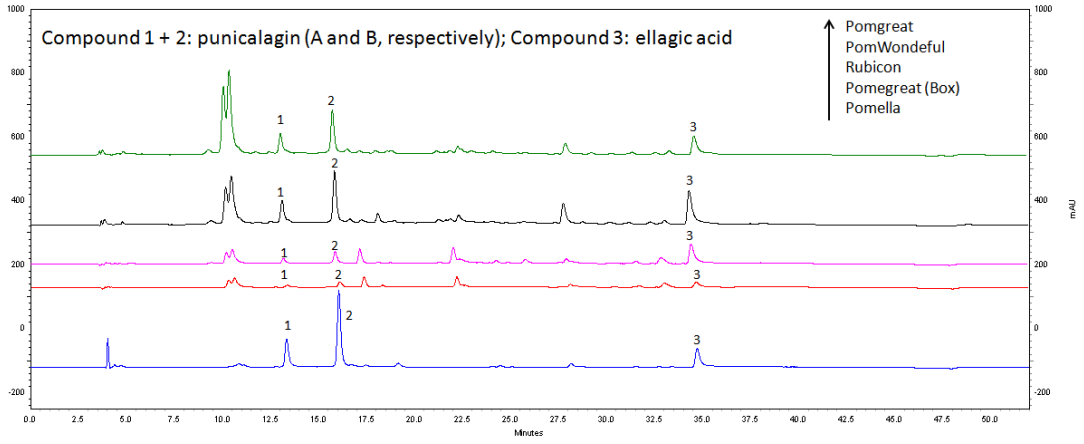
Relation Between Commercial Pomegranate Juice and Pomella®

- 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®

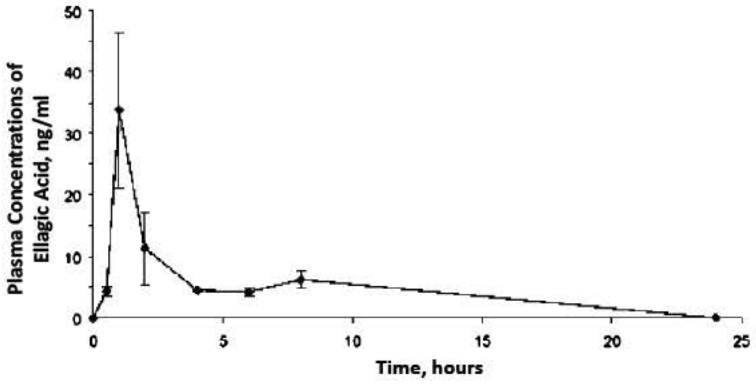


Figure 5. LC-MS extracted ion chromatograms showing the presence of ellagitannin metabolites in human plasma. (A) ellagic acid, (B) urolithin A, (C) hydroxyurolithin A, (D) urolithin B, (E) urolithin A-glucuronide, (F) dimethyl ellagic acid glucuronide.

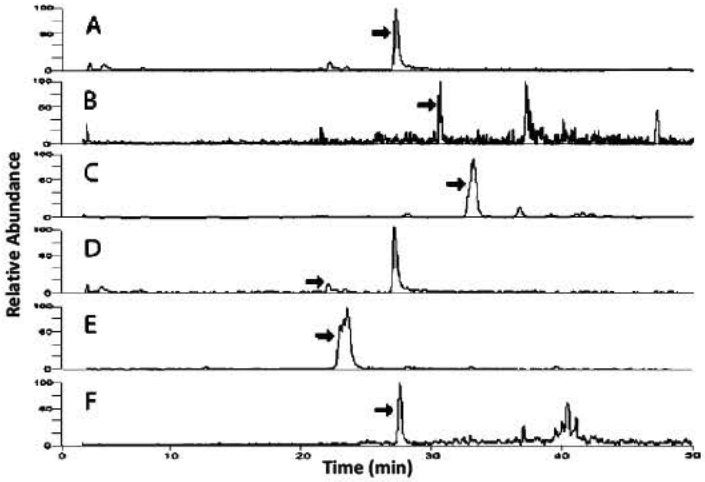
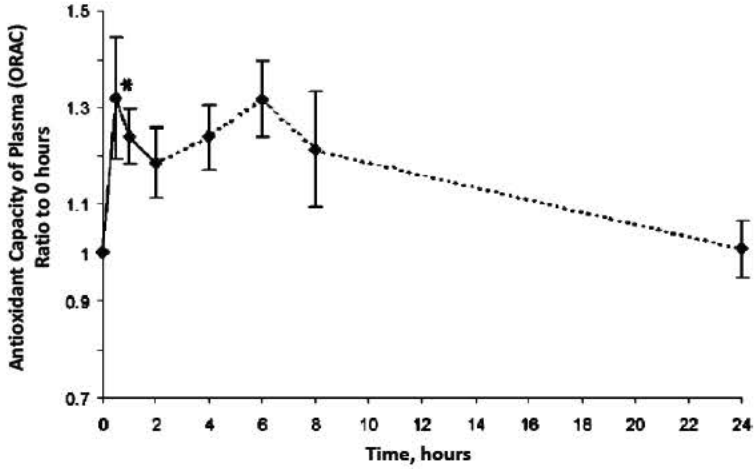


Figure 6. Antioxidant capacity in plasma after the consumption of 800 mg of Pomella®. Values significantly different ($p \leq 0.05$) from baseline are marked with an asterisk.



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).

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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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10/7/2022

Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
United States Food and Drug Administration
stephen.difranco@fda.hhs.gov

RE: GRN 1064 Pomegranate Extract - Items for Clarification
II1083.2-VER.8

Dear Dr. DiFranco,

REJIMUS, INC. received your email dated 8/15/22 regarding a request for clarification due to sixteen (16) issues that were noted during the review of GRN 1064 on Pomegranate Extract. Another email dated 9/29/22 was recently received regarding additional feedback from the toxicology team, that will be addressed in a follow-on response to this update.

As requested, responses to the majority of the requested information are presented in this report, while the remaining items are in progress or are awaiting further clarification from the Agency.

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

Sincerely,

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

TABLE OF CONTENTS

CONFIRMATION REQUESTED

Concern 1

Verdure Sciences provided a CAS Registry Number (CAS RN) 57961-57-9 for pomegranate fruit extract (p. 7), but we were not able to confirm that this CAS RN corresponds to your ingredient. Please provide a correct CAS RN for the pomegranate extract, if available.

Response

The correct CAS number is 84961-57-9.

Concern 2

Based on the description on p. 8, ethanol should be the only solvent used in the manufacturing process of pomegranate fruit extract. Verdure Sciences proposed a specification for residual solvents that complies with USP <467> (Table 2, p. 10). We note that USP <467> is a standard for the residual organic volatile chemicals that are used in the manufacture of drug substances or excipients, or in the preparation of drug products, and acceptance limits are based on "permitted daily exposures." Assuming that ethanol is the only solvent used in the manufacture of pomegranate fruit extract and considering that the extract is intended to be used in food, we request that the specification parameter be listed as "ethanol", not "residual solvents", and that the specification limit be based on quantification of the residual ethanol in representative batches of the final pomegranate fruit extract.

Response

REJIMUS, INC. has revised the Verdure specification and removed "Residual Solvents" and replaced it with Ethanol. Due to the fact that this is a spray-dried product, the volume of residual ethanol is expected to be extremely low. At this time the specification will state that the residual ethanol must be ≤ 1000 ppm, which is less than the stated limit of ≤ 5000 ppm in USP<467> for class 3 solvents such as ethanol. Should the data allow for lowering this limit, it shall be performed as a controlled change to the final specification.

[Reference Attachment II1083.2-VER.8-A1]

Concern 3

Verdure Sciences proposed a specification for pesticide residues that complies with USP <561> (Table 2, p. 10).

3a We note that according to the USP <561> standard, "The limits contained herein, therefore, are *not* applicable in the United States when articles of botanical origin are labeled for food purposes."

3b Given that tolerances for pesticide residues in pomegranate fruit are listed in 40 CFR 180, we request that Verdure Sciences address possible pesticide contamination based on pomegranate agricultural practices rather than the pesticide list in USP <561>. Please discuss the pesticides that

may be used in the production (harvest and post-harvest) of pomegranate fruit and steps taken to ensure the absence of pesticide residues in the pomegranate fruit extract.

3c We note that residual pesticides are not expected to be present in ingredients manufactured using food-grade plant materials produced in accordance with good agricultural practices. Please confirm that pesticide residues are not expected to be present in the pomegranate fruit extract or clarify the basis for proposing a pesticide specification for the pomegranate extract.

Response

We acknowledge that pesticide residues for pomegranate fruit are listed in 40 CFR 180. However, Verdure Sciences has confirmed that pesticides are not used during harvest and post-harvest of the pomegranate fruit nor is grown adjacent to any other crops using pesticides. Moreover, the pomegranate fruit is washed with water to remove dust and debris of any kind prior to further processing. Owing to no pesticides being used and additional washing of the fruit prior to manufacturing of the ingredient, the risk of pesticides in the ingredient is considered negligible.

Concern 4

We note that the proposed specification limits for heavy metals are ≤ 2 mg/kg while the levels of heavy metals in each of the three batches are reported to be < 0.01 mg/kg (Table 2, p.10). We request that Verdure Sciences consider lowering the specification limits for heavy metals to reflect the results of batch analyses and to be as low as possible.

Response

The heavy metal specification for Pomella has been revised to reflect that the results of the testing be as low as feasible.

[Reference Attachment II1083.2-VER.8-A1]

Concern 5

Verdure Sciences provided the results from the analyses of three representative batches of the pomegranate fruit extract (Table 2, p. 10). Please clarify if the analytical results are derived from consecutive or nonconsecutive batches. If the analytical results are from consecutive batches, please provide the results from analyses of a minimum of three nonconsecutive batches.

Response

The data from the representative batches that are presented in the dossier are from non-consecutive batches. Verdure has provided an additional certificate of analysis that is representative of a non-consecutive batch.

[Reference Attachment II1083.2-VER.8-A1]

Concern 6

In Part 1 (p. 4), Verdure Sciences stated that pomegranate fruit extract is intended to be used as an ingredient in "dairy products, non-alcoholic juice beverages, and chocolate candy" at levels up to 50 mg per serving. In Part 3 (p. 12), Verdure Sciences stated that the ingredient is intended to be used in fluid milk products and omitted the two other food categories. However, Verdure Sciences provided dietary exposure estimates from the intended uses of the ingredient in fluid milk, juices, and chocolate candy (Part 3, pp. 12-20). To clarify the intended uses of the ingredient, please provide representative NHANES food codes that were used for the dietary exposure estimates. In addition, please provide corresponding maximum use levels of pomegranate fruit extract in each food codes expressed in mg/kg.

Response

As a clarification, juices and chocolate candy are additional food categories where the ingredient is intended to be used in as specified in Part 1 of the notification. These additional two food categories were inadvertently omitted in Part 3 of the notification. Representative NHANES food codes used in the dietary exposure for each food category, inclusive of the three food categories, are provided. Each of the food codes are combined in the cumulative exposure of each of the food category and are identified in the respective attached cited below to this response. Owing to this cumulative exposure for each food category, the maximum use levels of pomegranate fruit extract in each of the food categories are shown below, based on the total population 90th percentile exposure and human body weight of 60 kg:

1. Dairy products are 1.55 mg/kg bw/day
2. Juices are 1.63 mg/kg bw/day
3. Chocolate candy is 1.32 mg/kg bw/day

Based on the maximum use levels of pomegranate fruit extract in the three food categories, the levels are well below the 310 mg/day maximum 90th percentile intake (5.18 mg/kg bw/day). The calculations above shows that the intake at the 90th percentile is combined at 4.5 mg/kg bw/day.

[Reference Attachment II1083.2-VER.8-A2]

Concern 7

Verdure Sciences used recent NHANES 2017-2018 consumption data for dairy milk, juice, and chocolate candy food categories to estimate the "*per capita*" dietary exposure to pomegranate fruit extract from the intended uses to be 310 mg/d at the 90thpercentile for US male adults aged 20 years and older (pp. 20-21). We note that typically a more conservative "eaters-only" dietary exposure is considered in the safety assessment. Please provide dietary exposures to pomegranate fruit extract from all intended uses as well as the total dietary exposure to pomegranate polyphenols (from background sources and the intended uses of pomegranate fruit extract), for the US population aged 2 years and older at the mean and 90th percentile.

Response

IN PROGRESS

Concern 8

Please provide the details of the literature search conducted in preparation of notice, such as the resource databases (e.g., PubMed, Web of Science), the search terms used, and the time span the literature search covered (e.g., month/year to present).

- Please keep in mind if additional literature searches are performed to supplement the original notice in an addendum, then information on the details (see above) and dates of these searches should also be included in the notifier's response to the Question 8.

Response

The literature search for the preparation of this notice for the intended uses was conducted on 11/13/2019 until the GRAS Notification submission of 03/25/2022. Google Scholar, Pubmed and NIH National Library of Medicine were used as the resource databases during the literature research using the search terms of "pomegranate", "polyphenols", "pomegranate juice", "pomegranate toxicity", "pomegranate powder", and "pomegranate clinicals." The rest of the literature or study information was provided by the sponsor as part of the GRAS Dossier development efforts. Therefore, the literature review was current at the time of the GRAS determination and FDA notification.

Concern 9

Please discuss the published information on the genotoxicity, mutagenicity, and cytotoxicity of whole fruit pomegranate extract and its constituents and metabolites in normal cells or organisms. If fruit pomegranate extract shows cytotoxicity, please discuss why its consumption is safe despite the cytotoxicity.

Related Inquiry. Your request centers around Genotoxicity, Cytotoxicity and Mutagenicity of the whole fruit pomegranate extract. Can you please provide more clarity or understanding of what data or explanation is being sought specifically?

- To address this question, please search and review available published literature to identify findings in normal cells or organisms on the genotoxic, mutagenic, and/or cytotoxic activities associated with exposure to pomegranate extract and/or its principal constituents including findings from in vitro tests. Please cite and briefly describe any of these effects that are documented. Positive genotoxicity, cytotoxicity and mutagenicity results argue against the GRAS conclusion. Therefore, briefly discuss the findings, and explain why those findings are not relevant in the context of your extract. In other words, justify why you can still draw a GRAS conclusion. You may pay attention to the nature of the extracts reported in such studies and if they are equivalent to your extract.

Response

IN PROGRESS

Please note, as of the time of this writing this response, there was no literature identified that indicated any levels of cytotoxicity of pomegranate whole fruit extract against healthy human cells. There was

literature found with indication of cytotoxicity in specific cancer cells that had certain genes activated, whereby polyphenols contained in pomegranate would initiate an apoptosis pathway; however, none of the studies we identified reported such activity being observed in normal cells or cell lines, thus was intentionally not included in the original notification.

Concern 10

Please review and discuss the available published literature on the allergenicity of pomegranate, and whole fruit pomegranate extract and its constituents. In other words, please discuss why allergenicity is not a safety concern for the consumption of fruit pomegranate extract.

Related Inquiry. Similar to question 9, can you please clarify as to the level of detail that is preferred by the reviewers?

- Food allergenicity is an important consideration for some food ingredients, including fruit extracts. Because no information on the noted allergenicity was provided in the notice, it needs to be included for completeness of the notifier's safety evaluation. To address this question, please search and review available published literature to identify information or findings on the allergenicity of pomegranate, and pomegranate extract and its principal constituents (such as those identified in the notice). Please briefly describe the published information on allergenicity of these plant substances including case reports, or state the paucity of this documented information for each substance. Please also discuss how the described findings contribute to your safety determination for the consumption of pomegranate extract. In your discussion you may take into consideration that there is probably no whole fruit extract that can be guaranteed to be totally free of the risk of allergenicity to every individual in the world. Also, take into consideration that pomegranate whole fruit extract has been consumed over a long period of time, and that it is not one of the major allergens.

Response

IN PROGRESS

Concern 11

Some information on the absorption and metabolism of whole fruit pomegranate extract and its constituents is provided in the notice. Please provide a comprehensive yet brief overview of the absorption, distribution and metabolism and excretion (ADME) of whole fruit pomegranate extract, including its primary constituents.

Related Inquiry. REJIMUS would like additional clarification on this question. Are there specific constituents or metabolites that are of concern to the Agency?

- The ADME discussion in the notice on the whole fruit pomegranate extract ingredient and its principal constituents is incomplete and needs supplementation. In the GRAS notification process, the notifier is responsible for a comprehensive identification and review of several aspects of the properties and the potential concerns of exposure to the GRAS food ingredient. Therefore, ADME information is important, such as the metabolites, their excretion, elimination

half-life etc. Therefore, please briefly discuss the information that is out there in the public domain.

Response

IN PROGRESS

Concern 12

Please briefly address, using published literature, if the proposed 90th percentile consumption of fruit pomegranate extract for long periods of time could lead to any drug interactions, and discuss why such interactions do not pose a safety concern for the concerned subpopulations.

Related Inquiry. REJIMUS would like additional clarification of the concern and the area of evaluation.

- There is good body of published literature showing that the consumption of some fruit juices and/or their constituents, including pomegranate, alters the pharmacokinetics of many drugs used by humans (i.e., food-drug interactions). Please briefly review any published findings that address the possibility and nature of pomegranate fruit extract, or its constituents causing food-drug interactions and include discussion of such interactions on any potential subpopulations, particularly on long-term consumption of the pomegranate whole fruit extract. Please justify your GRAS conclusion in light of such information.

Response

IN PROGRESS

Concern 13

Please note that the conclusion (PDF p. 27; under Acute Toxicity Studies) on the safe level of human consumption using the LD50 as the NOAEL and employing 100 as the safety factor is a conceptually erroneous approach in food safety assessment, and should not be used to justify the proposed 90th percentile EDI.

Related Inquiry. REJIMUS would like additional clarification on this point to be able to provide the most adequate response.

- Safe level of human consumption of food ingredients is not determined based on acute toxicity studies for several reasons that are well established in the assessment of food ingredient safety. toxicology. Hence, we focus on briefly explaining our comment. Acute tox studies typically involve a single dose (or multiple doses if the desired dose cannot be administered all at once) administered within 24 hours. In the safety assessment for food ingredients, the NOAEL is determined from longer term studies such as subchronic and chronic studies performed with multiple doses. These studies more accurately reflect how the body handles the disposition of an ingredient after repeated use like how a food ingredient would be used. ADI is determined from the NOAEL using the default safety factor of 100 (10 x 10), which may change depending on the circumstances. Acute tox studies are often performed to determine the LD50 (a dose where 50% of the treated animals die) or some other measures of mortality (e.g., LD10, LD25). Acute tox

studies also help determine the dose for the longer-term studies. In this case, it can be stated that the value you described as an LD50 was something like an 'acute NOAEL'; an application of a safety factor to this value represents an acute toxicity reference value or something like an 'acute ADI'. Therefore, as a theoretical argument, if one wants to determine the ADI for chronic exposure from the NOAEL from an acute study, the safety factor would be several thousands, not a 100. In reality and as a routine practice in food ingredient safety assessment, determination of NOAEL, ADI, etc. using acute tox study data is not done for evaluation of chronic exposure and should never be attempted for the reasons discussed above.

Response

IN PROGRESS

Concern 14

NOAEL/Safety Factors represents an allowable daily intake level or ADI expressed as mg/kg bw/day. This ADI as mg/kg bw/day could be further transformed into mg/person/day using 60 kg as the average adult body weight. This has not been clearly described for the subchronic toxicity study (p. 28 of the PDF, first paragraph). Instead, the way it has been written in the GRN refers to the derived ADI instead as a NOAEL. Please correctly describe these terms in reference to discussion of the subchronic study. Please also indicate the considered safety factors that contributed to the final overall safety factor used in the ADI derivation. Next, to evaluate the proposed total estimated daily intake (or EDI) of whole fruit pomegranate extract, the EDI should be compared to the ADI. In the case of a GRAS safety evaluation, the 90th percentile EDI of the subject of this notice should fall below this ADI.

Response

IN PROGRESS

Concern 15

Please discuss if the ADI derived from the NOAEL of the identified pivotal subchronic study justifies the proposed 90th percentile EDI of the ingredient that is the subject of this GRAS notice. In this discussion, please state if the proposed 90th percentile EDI is less than the derived ADI.

Related Inquiry. Is this question in relation to the terminology that was used in the write up, or is there an additional concern?

- The misuse of the so-called "terminology" in the safety evaluation in the narrative of the GRAS notice shows improper usage of the principal concepts of safety analysis for food ingredients. Thus, corrections in the description of the toxicology findings and the relevant reference values and related calculations (e.g., NOAEL, ADI) are warranted to have the notifier's safety evaluation deemed adequate and technically accurate. The safety evaluation in the notice is also deficient because the analysis was not complete. To determine the safety of the ingredient, you also need to compare the derived ADI for extended exposure to a substance to the 90th percentile total estimated chronic daily intake (EDI) of your food ingredient (expressed in the same units). Typically, the EDI should be lower than the ADI. This comparison is required as part of your safety

analysis and conclusions on the proposed use of the food ingredient. The outcome of this comparison serves to identify potential safety concerns with the proposed food ingredient exposures and its inclusion allows for a complete safety analysis. Next, it also should be noted that the findings of human studies discussed appeared to only administer pomegranate extract for short durations of exposure and often in individuals in varying health/disease states. These factors should be acknowledged when discussing the contribution of these study findings to the overall safety assessment for the food ingredient. In sum, the noted issues on the accuracy, adequacy, and completeness of the discussion of the safety evaluation performed and the related conclusions drawn is a concern and should be the focus of the response to this question.

Response

IN PROGRESS

Concern 16

On p 25 in the narrative section, a study that evaluated the metabolism of ingested whole fruit pomegranate extract in humans is discussed. Verdure Sciences explains the large variability seen between individuals in the plasma levels of an extract metabolite (see Figure 4) is due to noncompliance of certain study subjects to the study diet protocol. With respect to this stated conclusion, please address the following:

(a) Verdure Sciences has surmised non-compliance as the reason for the large variability seen between individuals in the plasma levels of an extract metabolite. However, the noncompliance hypothesis is difficult to accept because it is an assumption without any apparent basis. The study authors or Verdure Sciences did not explain how such a noncompliance was determined or could lead to a plasma spike of a metabolite after 24 hours. Instead, inter-individual variability in metabolism, particularly due to inter-individual genetic differences, is well-recognized now. Individual variability in the metabolism of dietary polyphenols has also been reported (e.g., Certa et al., 2005[1]). Please discuss the nature, basis, and role of individual variability with respect to the metabolism of whole fruit pomegranate extract. Please include discussion of the contribution of gut microbiota.

Response

IN PROGRESS

Attachments:

II1083.2-VER.8-A1	Non-consecutive batch Certificates of Analysis for Pomella
II1083.2-VER.8-A2	Representative NHANES food codes

Conclusion

We sincerely appreciate this opportunity to clarify the information submitted and look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions on the above responses upon review, we will address those promptly. We will continue compiling responses to the remaining concerns to revert a second response as soon as possible.

Attachment
II1083.2-VER.8-A1

CERTIFICATE OF ANALYSIS

POMELLA ®

LATIN NAME:	COMMON NAME:	HARVEST SEASON:	LOT NUMBER:
Punica granatum	Pomegranate	October - December[1]	LPR1EP1913K03
ORIGIN:	**PLANT PART USED:**	**HARVEST METHOD:**	**MFG. DATE:**
India	Whole Fruit	Cultivated	October 2019

Product code: POM030EPPH

PHYSICAL CHARACTERISTIC	SPECIFICATION	TEST METHOD	RESULTS (-)
Identification	Positive	TLC/HPLC (QC/TEC/078)	Confirms
Appearance	Dry Powder	Visual (QC/TEC/153)	Confirms
Color	Yellowish Brown to Brown[2]	Visual (QC/TEC/153)	Confirms
Odor	Slight Earthy	Organoleptic (QC/TEC/153)	Confirms
Taste	Astringent	Organoleptic (QC/TEC/153)	Confirms
Particle Size	NLT 90.00% thru 80 mesh	USP <786>	100%
Bulk Density	NLT 0.30 g/mL	USP <616>	0.40 g/mL
Tap Density	NLT 0.40 g/mL	USP <616>	0.50 g/mL
CHEMICAL ANALYSIS	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Assay for Actives			
a. Punicalagins	NLT 30.00%	HPLC (QC/TEC/078)	30.17%
b. Polyphenols	NLT 50.00%	UV-Vis (QC/TEC/031)	57.36%
Loss on Drying	NMT 6.00%	USP <731>	4.18%
IMPURITIES	**SPECIFICATION**	**TEST METHOD**	**RESULTS (+)**
Lead	< 0.1 ppm	USP <233> ICP-MS	< 0.010 ppm (ICP-MS)
Mercury	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Arsenic	< 0.1 ppm	USP <233> ICP-MS	0.014 ppm (ICP-MS)
Cadmium	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Pesticides Residue	USP <561> Screen	USP <561>	Complies
Residual Ethanol	< 1000 ppm	USP <467>	Complies
MICROBIOLOGY	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Total plate count	< 10000 cfu/g	USP <2021>	30 cfu/g
Yeast & mold	< 1000 cfu/g	USP <2021>	10 cfu/g
Escherichia coli	Absent/10g	USP <2022>	Absent/10g
Salmonella	Absent/10g	USP <2022>	Absent/25g
Coliform	< 100 cfu/g	USP <2021>	<10 cfu/g
S. Aureus	Absent/10g	USP <2022>	Absent/10g
Enterobacteriaceae	< 100 cfu/g	USP <2021>	<10 cfu/g

Herb Extract Ratio: 50:1 Extraction Solvent: 100% Ethanol Excipient: None

[1]Harvest season is subject to change based on environmental changes.
[2]Color of botanical products is subject to seasonal conditions and may vary from lot to lot.
(-) The result shown is from the supplier's Certificate of Analysis
(+) The result shown is from third party analysis
NOTE: Material has an inherent tendency to form clumps due to its hygroscopic nature.

Shelf Life: 48 months from date of manufacture
Storage: At room temperature, away from sunlight and moisture

Approved by: _ _ Date: September 16, 2022
V1.R13

VERDURE SCIENCES

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CERTIFICATE OF ANALYSIS

POMELLA ®

LATIN NAME:	COMMON NAME:	HARVEST SEASON:	LOT NUMBER:
Punica granatum	Pomegranate	October - December[1]	LPR1EP1912J11
ORIGIN:	**PLANT PART USED:**	**HARVEST METHOD:**	**MFG. DATE:**
India	Whole Fruit	Cultivated	September 2019

Product code: POM030EPPH

PHYSICAL CHARACTERISTIC	SPECIFICATION	TEST METHOD	RESULTS (-)
Identification	Positive	TLC/HPLC (QC/TEC/078)	Confirms
Appearance	Dry Powder	Visual (QC/TEC/153)	Confirms
Color	Yellowish Brown to Brown[2]	Visual (QC/TEC/153)	Confirms
Odor	Slight Earthy	Organoleptic (QC/TEC/153)	Confirms
Taste	Astringent	Organoleptic (QC/TEC/153)	Confirms
Particle Size	NLT 90.00% thru 80 mesh	USP <786>	100%
Bulk Density	NLT 0.30 g/mL	USP <616>	0.40 g/mL
Tap Density	NLT 0.40 g/mL	USP <616>	0.52 g/mL
CHEMICAL ANALYSIS	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Assay for Actives			
a. Punicalagins	NLT 30.00%	HPLC (QC/TEC/078)	30.32%
b. Polyphenols	NLT 50.00%	UV-Vis (QC/TEC/031)	55.08%
Loss on Drying	NMT 6.00%	USP <731>	4.30%
IMPURITIES	**SPECIFICATION**	**TEST METHOD**	**RESULTS (+)**
Lead	< 0.1 ppm	USP <233> ICP-MS	< 0.010 ppm (ICP-MS)
Mercury	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Arsenic	< 0.1 ppm	USP <233> ICP-MS	0.014 ppm (ICP-MS)
Cadmium	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Pesticides Residue	USP <561> Screen	USP <561>	Complies
Residual Ethanol	< 1000 ppm	USP <467>	Complies
MICROBIOLOGY	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Total plate count	< 10000 cfu/g	USP <2021>	<10 cfu/g
Yeast & mold	< 1000 cfu/g	USP <2021>	Absent
Escherichia coli	Absent/10g	USP <2022>	Absent/10g
Salmonella	Absent/10g	USP <2022>	Absent/25g
Coliform	< 100 cfu/g	USP <2021>	<10 cfu/g
S. Aureus	Absent/10g	USP <2022>	Absent/10g
Enterobacteriaceae	< 100 cfu/g	USP <2021>	<10 cfu/g

Herb Extract Ratio: 50:1 Extraction Solvent: 100% Ethanol Excipient: None

[1]Harvest season is subject to change based on environmental changes.
[2]Color of botanical products is subject to seasonal conditions and may vary from lot to lot.
(-) The result shown is from the supplier's Certificate of Analysis
(+) The result shown is from third party analysis
NOTE: Material has an inherent tendency to form clumps due to its hygroscopic nature.

Shelf Life: 48 months from date of manufacture
Storage: At room temperature, away from sunlight and moisture

Approved by: _ _ Date: September 16, 2022
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CERTIFICATE OF ANALYSIS

POMELLA ®

LATIN NAME:	COMMON NAME:	HARVEST SEASON:	LOT NUMBER:
Punica granatum	Pomegranate	October - December[1]	LPR1EP1914K08
ORIGIN:	**PLANT PART USED:**	**HARVEST METHOD:**	**MFG. DATE:**
India	Whole Fruit	Cultivated	October 2019

Product code: POM030EPPH

PHYSICAL CHARACTERISTIC	SPECIFICATION	TEST METHOD	RESULTS (-)
Identification	Positive	TLC/HPLC (QC/TEC/078)	Confirms
Appearance	Dry Powder	Visual (QC/TEC/153)	Confirms
Color	Yellowish Brown to Brown[2]	Visual (QC/TEC/153)	Confirms
Odor	Slight Earthy	Organoleptic (QC/TEC/153)	Confirms
Taste	Astringent	Organoleptic (QC/TEC/153)	Confirms
Particle Size	NLT 90.00% thru 80 mesh	USP <786>	100%
Bulk Density	NLT 0.30 g/mL	USP <616>	0.40 g/mL
Tap Density	NLT 0.40 g/mL	USP <616>	0.50 g/mL
CHEMICAL ANALYSIS	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Assay for Actives			
a. Punicalagins	NLT 30.00%	HPLC (QC/TEC/078)	30.41%
b. Polyphenols	NLT 50.00%	UV-Vis (QC/TEC/031)	56.73%
Loss on Drying	NMT 6.00%	USP <731>	3.95%
IMPURITIES	**SPECIFICATION**	**TEST METHOD**	**RESULTS (+)**
Lead	< 0.1 ppm	USP <233> ICP-MS	< 0.010 ppm (ICP-MS)
Mercury	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Arsenic	< 0.1 ppm	USP <233> ICP-MS	0.014 ppm (ICP-MS)
Cadmium	< 0.1 ppm	USP <233> ICP-MS	< 0.01 ppm (ICP-MS)
Pesticides Residue	USP <561> Screen	USP <561>	Complies
Residual Ethanol	<1000 ppm	USP <467>	Complies
MICROBIOLOGY	**SPECIFICATION**	**TEST METHOD**	**RESULTS (-)**
Total plate count	< 10000 cfu/g	USP <2021>	<10 cfu/g
Yeast & mold	< 1000 cfu/g	USP <2021>	Absent
Escherichia coli	Absent/10g	USP <2022>	Absent/10g
Salmonella	Absent/10g	USP <2022>	Absent/25g
Coliform	< 100 cfu/g	USP <2021>	<10 cfu/g
S. Aureus	Absent/10g	USP <2022>	Absent/10g
Enterobacteriaceae	< 100 cfu/g	USP <2021>	<10 cfu/g

Herb Extract Ratio: 50:1 Extraction Solvent: 100% Ethanol Excipient: None

[1]Harvest season is subject to change based on environmental changes.
[2]Color of botanical products is subject to seasonal conditions and may vary from lot to lot.
(-) The result shown is from the supplier's Certificate of Analysis
(+) The result shown is from third party analysis
NOTE: Material has an inherent tendency to form clumps due to its hygroscopic nature.

Shelf Life: 48 months from date of manufacture
Storage: At room temperature, away from sunlight and moisture

Approved by: _____ **Date: September 16, 2022**
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CERTIFICATE OF ANALYSIS

POMELLA ®

LATIN NAME:	COMMON NAME:	HARVEST SEASON:	LOT NUMBER:
Punica granatum	Pomegranate	October - December[1]	LPR1EP2003D30
ORIGIN:	**PLANT PART USED:**	**HARVEST METHOD:**	**MFG. DATE:**
India	Whole Fruit	Cultivated	April 2020

Product code: POM030EPPH

PHYSICAL CHARACTERISTIC	SPECIFICATION	TEST METHOD	RESULTS (-)
Identification	Positive	TLC/HPLC	Confirms
Appearance	Dry Powder	Visual	Confirms
Color	Yellowish Brown to Brown[2]	Visual	Confirms
Odor	Characteristic	Organoleptic	Confirms
Taste	Characteristic	Organoleptic	Confirms
Particle Size	NLT 90.00% thru 80 mesh	USP <786>	100 %
Bulk Density	NLT 0.30 g/mL	USP <616>	0.56g/mL
Tap Density	NLT 0.40 g/mL	USP <616>	0.68g/mL

CHEMICAL ANALYSIS	SPECIFICATION	TEST METHOD	RESULTS (-)
Assay for Actives			
a. Punicalagins	NLT 30.00%	HPLC	31.67%
b. Polyphenols	NLT 50.00%	UV-Vis	56.64%
Loss on Drying	NMT 6.00%	USP <731>	3.79%
Herb Extract Ratio	50:1	In-house specification	Confirms
Extraction Solvent	Alcohol	In-house specification	Confirms
Excipient	None	In-house specification	None

IMPURITIES	SPECIFICATION	TEST METHOD	RESULTS (+)
Lead	< 0.1 ppm	AAS/ICP-MS	0.012 ppm (ICP-MS)
Mercury	< 0.1 ppm	AAS/ICP-MS	< 0.01 ppm (ICP-MS)
Arsenic	< 0.1 ppm	AAS/ICP-MS	0.030 ppm (ICP-MS)
Cadmium	< 0.1 ppm	AAS/ICP-MS	< 0.01 ppm (ICP-MS)
Pesticides Residue	USP <561> Screen	USP <561>	Complies
Residual Ethanol	< 1000 ppm	USP <467>	Complies

MICROBIOLOGY	SPECIFICATION	TEST METHOD	RESULTS (-)
Total plate count	< 10000 cfu/g	USP	< 10 cfu/g
Yeast & mold	< 1000 cfu/g	USP	Absent
Escherichia coli	Absent/10g	USP	Absent
Salmonella	Absent/10g	USP	Absent
Coliform	< 100 cfu/g	USP	Absent
S. Aureus	Absent/10g	USP	Absent
Enterobacteriaceae	< 100 cfu/g	USP	Absent

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(+) The result shown is from third party analysis

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Shelf Life: 48 months from date of manufacture

Storage: At room temperature, away from sunlight and moisture

Approved by: _____ **Date: September 16, 2022**

V1.R13

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Attachment
II1083.2-VER.8-A2

Food Name	Food Code
Milk, NFS	11100000
Milk, whole	11111000
Milk, low sodium, whole	11111100
Milk, calcium fortified, whole	11111150
Milk, calcium fortified, low fat (1%)	11111160
Milk, calcium fortified, fat free (skim)	11111170
Milk, reduced fat (2%)	11112110
Milk, low fat (1%)	11112210
Milk, fat free (skim)	11113000
Milk, lactose free, low fat (1%)	11114300
Milk, lactose free, fat free (skim)	11114320
Milk, lactose free, reduced fat (2%)	11114330
Milk, lactose free, whole	11114350
Pomegranate, raw	63145010
Pomegranate juice, 100%	64126000
Grapefruit juice, 100%, freshly squeezed	61201010
Grapefruit juice, 100%, NS as to form	61201020
Grapefruit juice, 100%, canned, bottled or in a carton	61201220
Grapefruit juice, 100%, with calcium added	61201225
Grapefruit juice,100%, frozen, reconstituted	61201620
Orange juice, 100%, NFS	61210000
Orange juice, 100%, freshly squeezed	61210010
Orange juice, 100%, canned, bottled or in a carton	61210220
Orange juice, 100%, with calcium added, canned, bottled or in a carton	61210250
Orange juice, 100%, frozen, reconstituted	61210620
Orange juice, 100%, frozen, not reconstituted	61210720
Orange juice, 100%, with calcium added, frozen, reconstituted	61210820
Tangerine juice, 100%	61213220
Fruit juice blend, citrus, 100% juice	61213800
Fruit juice blend, citrus, 100% juice, with calcium added	61213900
Fruit juice, NFS	64100100
Fruit juice blend, 100% juice	64100110
Cranberry juice blend, 100% juice	64100200
Cranberry juice blend, 100% juice, with calcium added	64100220
Apple juice, 100%	64104010
Apple juice, 100%, with calcium added	64104030
Blackberry juice, 100%	64104600
Blueberry juice	64104610
Cranberry juice, 100%, not a blend	64105400
Grape juice, 100%	64116020
Grape juice, 100%, with calcium added	64116060
Papaya juice, 100%	64120010
Passion fruit juice, 100%	64121000
Pineapple juice, 100%	64124020

Prune juice, 100%	64132010
Strawberry juice, 100%	64132500
Watermelon juice, 100%	64133100
Beet juice	73105000
Carrot juice, 100%	73105010
Tomato juice, 100%	74301100
Tomato juice, 100%, low sodium	74301150
Tomato and vegetable juice, 100%	74303000
Tomato and vegetable juice, 100%, low sodium	74303100
Mixed vegetable juice	75132000
Celery juice	75132100
Vegetable and fruit juice, 100% juice, with high vitamin C	78101000
Fruit juice, acai blend	95342000
M&M's Almond Chocolate Candies	91700500
Almonds, chocolate covered	91700500
Caramel candy, chocolate covered	91703040
Caramel with nuts and cereal, chocolate covered	91703050
Caramel with nuts, chocolate covered	91703060
Rolo	91703070
Toblerone, milk chocolate with honey and almond nougat	91703150
TWIX Caramel Cookie Bars	91703200
TWIX Chocolate Fudge Cookie Bars	91703250
TWIX Peanut Butter Cookie Bars	91703300
Whatchamacallit	91703400
Espresso coffee beans, chocolate-covered	91703600
Milk chocolate candy, plain	91705010
Milk chocolate candy, with cereal	91705020
Kit Kat	91705030
Chocolate, milk, with nuts, not almond or peanuts	91705040
Milk chocolate candy, with fruit and nuts	91705050
Milk chocolate candy, with almonds	91705060
Chocolate, milk, with peanuts	91705070
Chocolate candy with fondant and caramel	91705090
Chocolate, semi-sweet morsel	91705200
Chocolate, sweet or dark	91705300
Chocolate, sweet or dark, with almonds	91705310
Mexican chocolate, tablet	91705500
Coconut candy, chocolate covered	91706000
Fondant, chocolate covered	91707010
Gumdrops, chocolate covered	91709000
Fudge, chocolate, chocolate-coated	91713010
Fudge, chocolate, chocolate-coated, with nuts	91713020
Fudge, chocolate	91713030
Fudge, chocolate, with nuts	91713040
Fudge, caramel and nut, chocolate-coated candy	91715000

SNICKERS Bar	91715100
Baby Ruth	91715200
100 GRAND Bar	91715300
Halvah, chocolate covered	91716110
Honey-combed hard candy with peanut butter, chocolate covered	91718050
Butterfinger	91718100
Butterfinger Crisp	91718110
Chocolate-flavored sprinkles	91718200
Marshmallow, chocolate covered	91723010
Nougat, with caramel, chocolate covered	91726110
MILKY WAY Bar	91726130
MILKY WAY MIDNIGHT Bar	91726140
MARS Almond Bar	91726150
Nougat, chocolate covered	91726410
3 MUSKETEERS Bar	91726420
3 Musketeers Truffle Crisp Bar	91726425
Nuts, chocolate covered, not almonds or peanuts	91727010
Nut roll, fudge or nougat, caramel and nuts	91728000
Peanuts, chocolate covered	91731000
M&M's Peanut Chocolate Candies	91731010
M&M's Peanut Butter Chocolate Candies	91731060
Peanut Bar, chocolate covered candy	91733200
Peanut butter, chocolate covered	91734000
Reese's Peanut Butter Cup	91734100
Reese's Sticks	91734300
Reese's Fast Break	91734400
Reese's Crispy Crunchy Bar	91734450
Raisins, chocolate covered	91739010
Sugar-coated chocolate discs	91746010
M&M's Milk Chocolate Candies	91746100
Sixlets	91746120
Easter egg, candy coated chocolate	91746150
M&M's Pretzel Chocolate Candies	91746200
Toffee, chocolate covered	91760100
Toffee, chocolate-coated, with nuts	91760200
Truffles	91760500
Dietetic or low calorie candy, chocolate covered	91770030

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Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
United States Food and Drug Administration
stephen.difranco@fda.hhs.gov

September 1, 2022

RE: Agenda for Teleconference on September 2, 2022
II1083.2-VER.9

Meeting Agenda

(Times are listed at EDT)

1:00pm - Introduction of respective team members

1:05pm - Roundtable discussion and clarification of requests

- REJIMUS, INC is proposing discussion of the following questions that were identified by Dr. DiFranco and his team at the FDA:
    - Question 9 – Your request centers around Genotoxicity, Cytotoxicity and Mutagenicity of the whole fruit pomegranate extract. Can you please provide more clarity or understanding of what data or explanation is being sought specifically?
    - Question 10 – Similar to question 9, can you please clarify as to the level of detail that is preferred by the reviewers?
    - Question 11 – REJIMUS would like additional clarification on this question. Are there specific constituents or metabolites that are of concern to the Agency?
    - Question 12 – REJIMUS would like additional clarification of the concern and the area of evaluation.
    - Question 13 – REJIMUS would like additional clarification on this point to be able to provide the most adequate response.
    - Question 14 – Is this question in relation to the terminology that was used in the write up, or is there an additional concern?

1:30pm - Wrap up.

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10/28/2022

Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
United States Food and Drug Administration
stephen.difranco@fda.hhs.gov

RE: GRN 1064 Pomegranate Extract - Items for Clarification (Second Response)
II1083.2-VER.10

Dear Dr. DiFranco,

This is a follow-up to the response submitted on 10/10/22 in regard to your email dated 8/15/22 regarding a request for clarification due to sixteen (16) issues that were noted during the review of GRN 1064 on Pomegranate Extract. Another email was also received dated 9/29/22 regarding additional feedback from the toxicology team.

The initial response (II1083.2-VER.8) was to address Concerns 1 – 6 and 8. Should you have any questions or concerns with the information provided in that response, please let us know, and we'll address that promptly.

This second response is to address the rest of the requested information (Concerns 7 and 9 – 16). Should you have any questions or concerns with this information, please let us know, and we'll be sure to address that promptly.

Sincerely,

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

TABLE OF CONTENTS

CONFIRMATION REQUESTED

Concern 7

Verdure Sciences used recent NHANES 2017-2018 consumption data for dairy milk, juice, and chocolate candy food categories to estimate the "*per capita*" dietary exposure to pomegranate fruit extract from the intended uses to be 310 mg/d at the 90thpercentile for US male adults aged 20 years and older (pp. 20-21). We note that typically a more conservative "eaters-only" dietary exposure is considered in the safety assessment. Please provide dietary exposures to pomegranate fruit extract from all intended uses as well as the total dietary exposure to pomegranate polyphenols (from background sources and the intended uses of pomegranate fruit extract), for the US population aged 2 years and older at the mean and 90th percentile.

Response

The following tables (Tables 1, 2, and 3) are the dietary exposures at the mean and 90th percentile to each of the intended use for pomegranate fruit extract based on NHANES data (2017-2018).

Table 1. 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)
Young Children	2 to 3	83.91 (291)	296.93 (16.71)	610.79 (27.63)
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				

Table 2. 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)
Young Children	2 to 3	60.92 (159)	203.76 (15.67)	374.95 (27.69)
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

Table 3. 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)
Young Children	2 to 3	14.56 (38)	7.72 (0.83)	16.09 (2.66)
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				

Table 4 provides the summary of the estimated daily intake of Pomella® Pomegranate Extract in each of the intended foods. The assumption is that every serving is augmented with one serving (50mg) of Pomella® Pomegranate Extract.

The calculation of the estimated daily intake of Pomella® Pomegranate Extract in Dairy Milk calculation is based upon the 50 mg serving multiplied by the cup-equivalent data obtained from the NHANES data in Table 1 above knowing that one serving is one cup of milk or 244g of fluid dairy milk according to the Economic Research Service of the USDA. The estimated daily intake of Pomella® Pomegranate Extract in juice is calculated based upon the 50 mg serving multiplied by the "g/day" data obtained from the NHANES data as shown in Table 2 owing that one serving of juice is 187g according to the Economic Research Service of the USDA. The estimated daily intake of Pomella® Pomegranate Extract in chocolate candies is calculated based upon the 50 mg serving multiplied by the "g/day" data obtained from the NHANES data as shown in Table 3 owing that one serving of chocolate is 30g according to the reference amounts customarily consumed (RACC).

Table 4. 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	Dairy Milk (mg)		Juices (mg)		Chocolate Candies (mg)	
		Mean	90th %	Mean	90th %	Mean	90th %
Young Children	2 to 3	60.85	125.16	54.48	100.25	12.87	26.82
Children	3 to 11	48.71	93.62	47.58	88.06	26.45	69.72
Female Teenagers	12 to 19	38.12	74.36	46.21	86.35	33.25	57.37
Male Teenagers	12 to 19	54.32	97.80	65.63	144.39	41.43	98.22
Female Adult	20 and up	36.69	73.95	47.02	87.03	34.98	78.48
Male Adults	20 and up	45.66	102.38	57.83	108.30	41.23	99.83
Total Population	All ages	44.70	92.71	51.89	97.73	35.90	79.17

Based on the test results using the highest total polyphenols and punicalagin in one of the COAs (88.83%), the estimated daily intake of total polyphenols for each of the proposed food is shown in Table 5.

Table 5. Summary of the Estimated Daily Intake of Total Polyphenols from Proposed Food-Use in the U.S. by Population Group (mg)

Population Group (Years)	Age Group	Dairy Milk (mg)		Juices (mg)		Chocolate Candies (mg)	
		Mean	90th %	Mean	90th %	Mean	90th %
Young Children	2 to 3	54.05	111.18	48.39	89.05	11.43	23.82
Children	3 to 11	43.27	83.16	42.27	78.22	23.49	61.93
Female Teenagers	12 to 19	33.86	66.05	41.05	76.70	29.54	50.96
Male Teenagers	12 to 19	48.25	86.87	58.29	128.26	36.80	87.25
Female Adult	20 and up	32.59	65.69	41.77	77.31	31.07	69.71
Male Adults	20 and up	40.56	90.94	51.37	96.02	41.23	36.62
Total Population	All ages	39.71	82.35	46.09	86.81	35.90	70.33

The cumulative exposure of Pomella® Pomegranate Extract in young children group aged 2 to 3 is 252.23 mg/d which is below the cumulative exposure of 310 mg/d at the 90thpercentile for US male adults aged 20 years and older of Pomella® Pomegranate Extract.

Concern 9

Please discuss the published information on the genotoxicity, mutagenicity, and cytotoxicity of whole fruit pomegranate extract and its constituents and metabolites in normal cells or organisms. If fruit pomegranate extract shows cytotoxicity, please discuss why its consumption is safe despite the cytotoxicity.

Related Inquiry. Your request centers around Genotoxicity, Cytotoxicity and Mutagenicity of the whole fruit pomegranate extract. Can you please provide more clarity or understanding of what data or explanation is being sought specifically?

- To address this question, please search and review available published literature to identify findings in normal cells or organisms on the genotoxic, mutagenic, and/or cytotoxic activities associated with exposure to pomegranate extract and/or its principal constituents including findings from in vitro tests. Please cite and briefly describe any of these effects that are documented. Positive genotoxicity, cytotoxicity and mutagenicity results argue against the GRAS conclusion. Therefore, briefly discuss the findings, and explain why those findings are not relevant in the context of your extract. In other words, justify why you can still draw a GRAS conclusion. You may pay attention to the nature of the extracts reported in such studies and if they are equivalent to your extract.

Response

Studies performed regarding the toxicology of pomegranate have been undertaken with a particular focus on the beneficial side of the noted activities of the constituents of the botanical. Evaluation of the genotoxicity found initially that the botanical does have genotoxic effects (Sanchez-Lamar et al. 2008). There is also evidence that there are beneficial effects to be derived in regard to these same properties as applied to preventive potential (Abdou et al. 2012). There is open debate regarding the extrapolation of the *in vitro* data to *in vivo* results (Turrini et al. 2015). The most recent studies have not shown specific constituents to hold genotoxic effects *in vivo (*Rodrigues da Silva et al. 2022). This is additionally shown in the literature surrounding cytotoxicity of the botanical and its primary constituents (Banerjee et al. 2012) (Sepehr et al. 2012) (Utami et al. 2021). While there is effect from pomegranate and its constituents that includes cytotoxic effects, the effects of particular note are not against healthy cells.

[Reference Attachment II1083.2-VER.10-A1, II1083.2-VER.10-A2, II1083.2-VER.10-A3, II1083.2-VER.10-A4, II1083.2-VER.10-A5, II1083.2-VER.10-A6, II1083.2-VER.10-A7]

Concern 10

Please review and discuss the available published literature on the allergenicity of pomegranate, and whole fruit pomegranate extract and its constituents. In other words, please discuss why allergenicity is not a safety concern for the consumption of fruit pomegranate extract.

Related Inquiry. Similar to question 9, can you please clarify as to the level of detail that is preferred by the reviewers?

- Food allergenicity is an important consideration for some food ingredients, including fruit extracts. Because no information on the noted allergenicity was provided in the notice, it needs to be included for completeness of the notifier's safety evaluation. To address this question, please search and review available published literature to identify information or findings on the allergenicity of pomegranate, and pomegranate extract and its principal constituents (such as those identified in the notice). Please briefly describe the published information on allergenicity of these plant substances including case reports, or state the paucity of this documented information for each substance. Please also discuss how the described findings contribute to your safety determination for the consumption of pomegranate extract. In your discussion you may take into consideration that there is probably no whole fruit extract that can be guaranteed to be totally free of the risk of allergenicity to every individual in the world. Also, take into consideration that pomegranate whole fruit extract has been consumed over a long period of time, and that it is not one of the major allergens.

Response

As with a variety of fruits, pomegranate exhibits rare instances of allergic reaction (Hassan et al. 2015). Reports of pomegranate allergy are very rare and often linked to pollen/fruit cross reactivity. While reactions to citrus seeds have been reported among cashew-allergic children, pomegranate seed allergy has not been well-described in tree-nut allergic patients (Zhang et al. 2021). The occurrence of such allergies is far from common as evidenced by the single case study found and shown in this report. There is some information that can be determined from the literature available. The allergic reactions Identified in the literature is seen in conjunction with allergies to other foods presenting as "Latex Food Syndrome" caused by the body confusing the proteins it encounters in food to that of latex proteins to which there is already sensitivity.

The allergenicities noted in the literature are not remotely common and are still under evaluation for elucidation of the causative agent of the allergic reaction. The present evidence in the literature research performed does not show significant incidence of such reactions to date given the history or consumption. The indications are that these are linked to IgE reaction at a relatively nominal molecular mass. The lack of incidence and elucidation of the causative entity alleviate notable concern over allergenicity to pomegranate. Owing to the infrequent nature of the allergic reactions and association with other IgE type fruit allergies, the potential for individual challenge for consumers ingesting this material is remote and thus not one of major allergens to be concerned with.

[Reference Attachment II1083.2-VER.10-A8, II1083.2-VER.10-A9]

Concern 11

Some information on the absorption and metabolism of whole fruit pomegranate extract and its constituents is provided in the notice. Please provide a comprehensive yet brief overview of the absorption, distribution and metabolism and excretion (ADME) of whole fruit pomegranate extract, including its primary constituents.

Related Inquiry. REJIMUS would like additional clarification on this question. Are there specific constituents or metabolites that are of concern to the Agency?

- The ADME discussion in the notice on the whole fruit pomegranate extract ingredient and its principal constituents is incomplete and needs supplementation. In the GRAS notification process, the notifier is responsible for a comprehensive identification and review of several aspects of the properties and the potential concerns of exposure to the GRAS food ingredient. Therefore, ADME information is important, such as the metabolites, their excretion, elimination half-life etc. Therefore, please briefly discuss the information that is out there in the public domain.

Response

Consumption of pomegranate and its constituents results in digestion and metabolizing these phytochemicals. Apart from the sugars contained in the fruit, chief among them fructose and maltose, there are a number of constituents that are of interest. Among these constituents of pomegranate are the ellagitannins which occur in other fruits as well. These are not absorbed but rather are subjected to the microbiota in the colon releasing ellagic acid which in turn is converted to urolithins which are absorbed into the circulatory system mainly as sulphate and glucuronide phase II metabolites. The dependence on the microflora providing the majority of the metabolism likely is one of the reasons for wide variation in the presence of these metabolites in the circulatory system. The initiation of the metabolism of the ellagitannins, and specifically ellagic acid, which is then gradually metabolized in the intestines producing, in sequence, urolithin D, and urolithin C ending with urolithin B and urolithin A. Additional metabolism occurs in the liver resulting in diglucuronides and/or sulfates giving a combination of metabolites secreted in the bile. Urolithins A and B along with ellagic acid are the metabolites that sufficiently metabolized to be excreted in urine where urolithins C and D are absorbed earlier in the intestine. The metabolite urolithin B seems to be the last degradation product of the metabolism of ellagic acid by intestinal flora. While urolithin B is found in feces, urolithin A is not. The latest information indicates that there are 13 identified urolithins derived from the metabolism of the ellagitannins present in pomegranate. As presently understood, the metabolism of ellagitannins (ETs) is highly dependent on the individual's ability to metabolize the basic compounds ingested (Garcia-Villalba et al. 2022). The variability among individuals and their ability to metabolize these compounds is shown in some of the studies performed measuring serum levels of these metabolites. The metabolites formed do not appear to have significant retention in tissues after metabolism and the resultant metabolites are excreted in both urine and feces.

[Reference Attachment II1083.2-VER.10-A10]

Concern 12

Please briefly address, using published literature, if the proposed 90th percentile consumption of fruit pomegranate extract for long periods of time could lead to any drug interactions, and discuss why such interactions do not pose a safety concern for the concerned subpopulations.

Related Inquiry. REJIMUS would like additional clarification of the concern and the area of evaluation.

- There is good body of published literature showing that the consumption of some fruit juices and/or their constituents, including pomegranate, alters the pharmacokinetics of many drugs used by humans (i.e., food-drug interactions). Please briefly review any published findings that address the possibility and nature of pomegranate fruit extract, or its constituents causing food-drug interactions and include discussion of such interactions on any potential subpopulations, particularly on long-term consumption of the pomegranate whole fruit extract. Please justify your GRAS conclusion in light of such information.

Response

Fruit juice-drug interaction has received wide attention with focus on the metabolism of a good many drugs by CYP3A4 and CYP2C9 enzymes. Current scientific literature has not completely resolved the issue of drug interaction from pomegranate juice specifically. The data presented in the literature indicates that pomegranate does not have the same interaction potential as for example grapefruit juice (Abdlekawy et al. 2017). It is also important to note that the comparative levels of consumption of juices in general, and more specifically pomegranate, are significantly higher than the proposed consumption levels of this ingredient. There is additional information that indicates a divergence in results form *in vitro* results found for some drugs (Hanley et al. 2012). The consideration of the potential interaction is one that should be considered potentially significant rather than clinically significant. The overall interaction profile of pomegranate, and specifically this pomegranate extract at the proposed levels herein this notice, with drugs is one that does not rise to a clinically significant level (Andrade et al.) based on our research.

[Reference Attachment II1083.2-VER.10-A11, II1083.2-VER.10-A12, II1083.2-VER.10-A13]

Concern 13

Please note that the conclusion (PDF p. 27; under Acute Toxicity Studies) on the safe level of human consumption using the LD50 as the NOAEL and employing 100 as the safety factor is a conceptually erroneous approach in food safety assessment, and should not be used to justify the proposed 90th percentile EDI.

Related Inquiry. REJIMUS would like additional clarification on this point to be able to provide the most adequate response.

- Safe level of human consumption of food ingredients is not determined based on acute toxicity studies for several reasons that are well established in the assessment of food ingredient safety. toxicology. Hence, we focus on briefly explaining our comment. Acute tox studies typically involve a single dose (or multiple doses if the desired dose cannot be administered all at once) administered within 24 hours. In the safety assessment for food ingredients, the NOAEL is determined from longer term studies such as subchronic and chronic studies performed with multiple doses. These studies more accurately reflect how the body handles the disposition of an ingredient after repeated use like how a food ingredient would be used. ADI is determined from the NOAEL using the default safety factor of 100 (10 x 10), which may change depending on the circumstances. Acute tox studies are often performed to determine the LD50 (a dose where 50% of the treated animals die) or some other measures of mortality (e.g., LD10, LD25). Acute tox studies also help determine the dose for the longer-term studies. In this case, it can be stated that the value you described as an LD50 was something like an 'acute NOAEL'; an application of a safety

Related Inquiry. Is this question in relation to the terminology that was used in the write up, or is there an additional concern?

- The misuse of the so-called "terminology" in the safety evaluation in the narrative of the GRAS notice shows improper usage of the principal concepts of safety analysis for food ingredients. Thus, corrections in the description of the toxicology findings and the relevant reference values and related calculations (e.g., NOAEL, ADI) are warranted to have the notifier's safety evaluation deemed adequate and technically accurate. The safety evaluation in the notice is also deficient because the analysis was not complete. To determine the safety of the ingredient, you also need to compare the derived ADI for extended exposure to a substance to the 90th percentile total estimated chronic daily intake (EDI) of your food ingredient (expressed in the same units). Typically, the EDI should be lower than the ADI. This comparison is required as part of your safety analysis and conclusions on the proposed use of the food ingredient. The outcome of this comparison serves to identify potential safety concerns with the proposed food ingredient exposures and its inclusion allows for a complete safety analysis. Next, it also should be noted that the findings of human studies discussed appeared to only administer pomegranate extract for short durations of exposure and often in individuals in varying health/disease states. These factors should be acknowledged when discussing the contribution of these study findings to the overall safety assessment for the food ingredient. In sum, the noted issues on the accuracy, adequacy, and completeness of the discussion of the safety evaluation performed and the related conclusions drawn is a concern and should be the focus of the response to this question.

Response

As described in the response for Concern 14, the subchronic study noted in the dossier concluded that a NOAEL for the product is at 600 mg/kg bw in rats (again, the maximum amount studied and again, no reports of adverse effects were noted). Therefore, the ADI derived from the NOAEL is calculated to be 360 mg/kg bw/day, assuming a 60 kg human and default safety factor of 100. The EDI of the notified substance is found to be 5.18 mg/kg bw/day, assuming a cumulative intake of 310.5 mg/day at the 90th percentile level which is conservative in that consumers of pomegranate juice would not likely be consumers of such juice with added potency. Therefore, the EDI is below the ADI, which ensures that the ingredient is reasonably expected to be safe.

Concern 16

On p 25 in the narrative section, a study that evaluated the metabolism of ingested whole fruit pomegranate extract in humans is discussed. Verdure Sciences explains the large variability seen between individuals in the plasma levels of an extract metabolite (see Figure 4) is due to noncompliance of certain study subjects to the study diet protocol. With respect to this stated conclusion, please address the following:

(a) Verdure Sciences has surmised non-compliance as the reason for the large variability seen between individuals in the plasma levels of an extract metabolite. However, the noncompliance hypothesis is difficult to accept because it is an assumption without any apparent basis. The study authors or Verdure Sciences did not explain how such a noncompliance was determined or could lead to a plasma spike of a metabolite after 24

hours. Instead, inter-individual variability in metabolism, particularly due to inter-individual genetic differences, is well-recognized now. Individual variability in the metabolism of dietary polyphenols has also been reported (e.g., Certa et al., 2005[1]). Please discuss the nature, basis, and role of individual variability with respect to the metabolism of whole fruit pomegranate extract. Please include discussion of the contribution of gut microbiota.

Response

The variability in the metabolism of polyphenols, particularly ellagitannins, among volunteers was supported by the presence of high and low metabolite excreters in each group (Cerda et al. 2005). An earlier human study validates this variability using the bioavailability and metabolism of the punicalagin in pomegranates (Cerda et al. 2004). Specific to pomegranates, this study showed that the excretion of urolithin B with respect to the punicalagin consumed had a wide range from 0.7 to 52.7%. It is suggested by Cerda et al. that urolithin B is biomarker compounds of ellagitannins, particularly of pomegranates, and that the colonic microflora are involved in the metabolism yielding high variability in the excretion of the metabolite. Hence, Cerda et al. determined that isoflavone metabolism by colonic microflora and individual genetic makeup are interrelated contributing factors.

[Reference Attachment II1083.2-VER.10-A14 and II1083.2-VER.10-A15]

Attachments:

II1083.2-VER.10-A1	Sanchez-Lamar A, Fonseca G, Fuentes JL, Cozzi R, Cundari E, Fiore M, Ricordy R, Perticone P, Degrassi F, De Calvia R. Assessment of genotoxic risk of *Punica granatum* L. (Punicaceae) whole fruit extracts *Journal of Ethnopharmacology*. 115 (2008) 416 - 422
II1083.2-VER.10-A2	Abdou HS, Salah SH, Boolesand HF, Abdel Rahim EA. Effect of pomegranate pretreatment on genotoxicity and hepatotoxicity induced by carbon tetra chloride (CCl_4) in male rats *Journal of Medicinal Plants Research*. Vol 6(17), pp 3370-3380, 9 May, 2012
II1083.2-VER.10-A3	Turrini E, Ferruzzi L, Fimognari C. Potential Effects of Pomegranate Polyphenols in Cancer Prevention and Therapy. *Oxidative Medicine and Cellular Longevity*. Vol. 2015, Article ID 938475 (19 pages).
II1083.2-VER.10-A4	Rodrigues da Silva A, Raion de Vasconcelos Alves R, Pedrosa da Silva S, Castelo Branco SJdS, Marinho AdO, Giselly dos Santos Souza T, Chagas CA, Guedes Paiva PM, Macario de Oliveira A, Napoleao TH. Acute toxicity and genotoxicity

	assessment of PgTeL, a lectin from pomegranate sarcotesta in mice. *South African Journal of Botany*. 2022, pages 1-8.
II1083.2-VER.10-A5	Banerjee N, Talcott S, Safe S, Mertens-Talcott SU. Cytotoxicity of Pomegranate Polyphenolics in Breast Cancer Cells in Vitro and Vivo – Potential Role of miRNA-27a and miRNA-155 in Cell Survival and Inflammation. *Breast Cancer Res Treat.* 2012 November, 136(1): 21-34.
II1083.2-VER.10-A6	Sepehr KS, Baradaran B, Mazandarani M, Khori V, Shaneh FZ. Studies on the Cytotoxic Activities of *Punica granatum* L. var. *spinosa* (Apple Punice) Extract on Prostate Cell line by Induction of Apoptosis*. ISRN Pharmaceutics*. Volume 2012, Article ID 547942, 6 pages.
II1083.2-VER.10-A7	Utami SM, Indarto D, Yudhani RD. Methanol Extract of Pomegranate Fruits Containing Ellagic Acid and Cytotoxicity in Vero Cell Line. *AIP Conf. Proc*. 2021, 070017-1–070017-5; https://doi.org/10.1063/1.5062815
II1083.2-VER.10-A8	Hassan AKG, Venkatesh YP. An overview of fruit allergy and the causative allergens. *Eur Ann Allergy Clin Immunol*. Vol 47, N 6, 180-187, 2015.
II1083.2-VER.10-A9	Zhang S, Baker M. M244 pomegranate seed allergy in a tree-nut allergic child. *Annals of Allergy, Asthma & Immunology*. Vol. 127: 5, November 2021, Page 5117
II1083.2-VER.10-A10	Garcia-Villalba R, Gimenez-Bastida JA, Cortes-Martin A, Avila-Galvez MA, Tomas-Barberan FA, Selma MV, Espin JC, Gonzalez-Sarrias A. Urolithins: a comprehensive update on their metabolism bioactivity, and associated gut microbiota. *Mol. Nutr Food Res.* 2022, 2101019.
II1083.2-VER.10-A11	Abdlekawy KS, Donia AM, Elbarbry F. Effects of Grapefruit and Pomegranate Juices on the Pharmacokinetic Properties of Dapoxetine and Midazolam. *Eur J Drug Metab Pharmacokinet*. (2017) 42: 397-405.

II1083.2-VER.10-A12	Hanley MJ, Masso G, Hermatz JS, Court MH, Greenblatt DJ. Pomegranate juice and pomegranate extract do not impair oral clearance of flurblprofen in human volunteers: Divergence from in vitro results. *Clin Pharmacol Ther*. 2012. November; 92(5): 651-657.
II1083.2-VER.10-A13	Andrade C. Potentially Significant Versus Clinically Significant Drug Interactions: Pomegranate Juice as a Case in Point. *J clin Psychiatry*. 2014; 75(4):e292-e293.
II1083.2-VER.10-A14	Cerdá B, Espin JC, Parra S, Martinez P, Tomás-Barberán FA. The potent in vitro antioxidant ellagitannins from pomegranate juice are metabolized into bioavailable by poor antioxidant hydroxy-6H-dibenzopyran-6-one derivatives by the colonic microflora of healthy humans. *Eur J Nutr.* 2004; 43:205-220.
II1083.2-VER.10-A15	Cerdá B, Tomás-Barberán FA, Espin JC. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: Identification of biomarkers and individual variability. *J Agric. Food Chem.* 2005; 53:227-235.

Conclusion

We sincerely appreciate this opportunity to clarify the information submitted and look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions on the above responses upon review, we will address those promptly.

All attachments (II1083.2-VER.10-A1 through II1083.2-VER.10-A15) have been removed in accordance with copyright laws. The removed reference citations can be found in the prior attachments list.

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11/9/2022

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Regulatory Review Scientist/Chemist
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
United States Food and Drug Administration
stephen.difranco@fda.hhs.gov

RE: GRN 1064 Pomegranate Extract - Items for Clarification (Second Response) – Additional Update
II1083.2-VER.10.1

Dear Dr. DiFranco,

Upon further review and recent discussions with the Agency on a similar matter, the following is an update to the Second Response submitted on 10/28/22, which further clarifies the ADI and EDI calculation, particularly the units of measure, in response to Concerns 14 and 15. The clarification is presented in the appropriate Concerns in bold.

Should you have any questions or concerns with this additional information or have additional requests based on the information provided so far, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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CONFIRMATION REQUESTED

Concern 14

NOAEL/Safety Factors represents an allowable daily intake level or ADI expressed as mg/kg bw/day. This ADI as mg/kg bw/day could be further transformed into mg/person/day using 60 kg as the average adult body weight. This has not been clearly described for the subchronic toxicity study (p. 28 of the PDF, first paragraph). Instead, the way it has been written in the GRN refers to the derived ADI instead as a NOAEL. Please correctly describe these terms in reference to discussion of the subchronic study. Please also indicate the considered safety factors that contributed to the final overall safety factor used in the ADI derivation. Next, to evaluate the proposed total estimated daily intake (or EDI) of whole fruit pomegranate extract, the EDI should be compared to the ADI. In the case of a GRAS safety evaluation, the 90th percentile EDI of the subject of this notice should fall below this ADI.

Update Response

The determination of the ADI for the product comes from the findings of the subchronic studies in animal models as described. The findings of the subchronic study noted in the inquiry indicate a NOAEL for the product at 600 mg/kg bw in the studied animal (rat model). The basis for the determination and the resultant establishment of an ADI derived is as follows:

The subchronic study noted in the dossier concluded that a NOAEL for the product is at 600 mg/kg bw in rats (again, the maximum amount studied and again, no reports of adverse effects were noted). Therefore, the ADI derived from the NOAEL is calculated to be **360 mg/day**, assuming a 60 kg human and default safety factor of 100. The EDI of the notified substance is found to be 5.18 mg/kg bw/day, assuming **a 60kg human with** a cumulative intake of 310.5 mg/day at the 90th percentile level which is conservative in that consumers of pomegranate juice would not likely be consumers of such juice with added potency. Therefore, the EDI is below the ADI, which ensures that the ingredient is reasonably expected to be safe.

Concern 15

Please discuss if the ADI derived from the NOAEL of the identified pivotal subchronic study justifies the proposed 90th percentile EDI of the ingredient that is the subject of this GRAS notice. In this discussion, please state if the proposed 90th percentile EDI is less than the derived ADI.

Related Inquiry. Is this question in relation to the terminology that was used in the write up, or is there an additional concern?

- The misuse of the so-called “terminology” in the safety evaluation in the narrative of the GRAS notice shows improper usage of the principal concepts of safety analysis for food ingredients. Thus, corrections in the description of the toxicology findings and the relevant reference values and related calculations (e.g., NOAEL, ADI) are warranted to have the notifier’s safety evaluation deemed adequate and technically accurate. The safety evaluation in the notice is also deficient because the analysis was not complete. To determine the safety of the ingredient, you also need to compare the derived ADI for extended exposure to a substance to the 90th percentile total estimated chronic daily intake (EDI) of your food ingredient (expressed in the same units).

Typically, the EDI should be lower than the ADI. This comparison is required as part of your safety analysis and conclusions on the proposed use of the food ingredient. The outcome of this comparison serves to identify potential safety concerns with the proposed food ingredient exposures and its inclusion allows for a complete safety analysis. Next, it also should be noted that the findings of human studies discussed appeared to only administer pomegranate extract for short durations of exposure and often in individuals in varying health/disease states. These factors should be acknowledged when discussing the contribution of these study findings to the overall safety assessment for the food ingredient. In sum, the noted issues on the accuracy, adequacy, and completeness of the discussion of the safety evaluation performed and the related conclusions drawn is a concern and should be the focus of the response to this question.

Update Response

The subchronic study noted in the dossier concluded that a NOAEL for the product is at 600 mg/kg bw in rats (again, the maximum amount studied and again, no reports of adverse effects were noted). Therefore, the ADI derived from the NOAEL is calculated to be **360 mg/day**, assuming a 60 kg human and default safety factor of 100. The EDI of the notified substance is found to be 5.18 mg/kg bw/day, assuming **a 60kg human with** a cumulative intake of 310.5 mg/day at the 90th percentile level which is conservative in that consumers of pomegranate juice would not likely be consumers of such juice with added potency. Therefore, the EDI is below the ADI, which ensures that the ingredient is reasonably expected to be safe.

Conclusion

We sincerely appreciate this opportunity to clarify the information submitted so far as part of this review and we look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions or requests on the above responses or the prior responses, please let us know at your earliest convenience and we will do everything we can to address those promptly.

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4/19/2023

Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist
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RE: GRN 1064 Pomegranate Extract – Toxicology-Related Questions
II1083.2-VER.11

Dear Dr. DiFranco,

REJIMUS, INC. received your email dated 3/8/23 regarding additional four (4) toxicology questions owing to the responses from 10/7/22, 10/28/22, and 11/09/22. An additional three (3) items were received on 3/24/23. Several responses are included herein, and for the ones identified that remain to be addressed owing to the Sponsor obtaining the required information, we are planning to provide the final responses on or before Friday, April 28th, 2023.

Should you have any questions or concerns with this additional information or have additional requests based on the information provided so far, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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TOXICOLOGY-RELATED QUESTIONS (RECEIVED 3/8/23)

Question 1

FDA's question on the literature search has not been addressed adequately before. Hence, we have a follow up concern that needs to be clearly addressed.

Concern to be addressed on literature search:

Please confirm (by stating clearly) whether the literature on the safety of pomegranate extract, published since your last literature review on this subject, has uncovered any information that would contradict your GRAS conclusion. A clear statement (a sentence or two) to that effect should be adequate.

Response

An additional literature review was performed in April 2023, since the last literature review performed in March 2022 regarding the safety of pomegranate extract. Different publication search platforms such as PubMed, American Journal of Medicine, ClinicalTrials.gov and Google Scholar were used with keywords "Pomegranate, Pomegranate extract," "safety," "adverse effects," and "clinical trials." The summary of the updated literature search is shown below. The results of this additional literature produced no information that would have contradicted or have been inconsistent with the GRAS conclusion.

Reference	Study Title	Subjects	Dose	Duration	Summary of Safety
Paller et al. (2013)	A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer.	95 patients	1000 mg of pomegranate extract or 3000mg of pomegranate extract	18 months	No serious adverse events were reported. Adverse effects observed in the study were gastrointestinal. There were cardiac-related adverse events, but the authors deemed it not related to the product.

Reference	Study Title	Subjects	Dose	Duration	Summary of Safety
Adel-Mehraban et al. (2022)	Effects of pomegranate supplement on menopausal symptoms and quality of life in menopausal women: a double-blind randomized placebo-controlled trial	78 women	Pomegranate supplement containing 787.5 mg gallic acid equivalent/g and 0.86 mg flavonoids.	3 weeks	No adverse effects were observed.
Pantuck et al. (2015)	A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer	183 human subjects	8 oz of pomegranate liquid extract	12 months	"Majority of adverse events (AEs) were of moderate or mild grade, and the overwhelming majority of AEs were judged as unrelated (87%) or unlikely related (9%) to study product in all groups"
Dormal et al. (2022)	Evaluation of a dietary supplementation combining protein and a pomegranate extract in order people: a safety study	30 subjects	650 mg pomegranate extract	3 weeks	No serious adverse effects and all other adverse effects were deemed not related to the product
Mirmiran et al. (2010)	Effect of pomegranate seed oil on hyperlipidaemic subjects: a double-blind placebo-controlled clinical trial	51 subjects	400 mg of pomegranate seed oil capsule	4 weeks	No adverse effects observed.

Reference	Study Title	Subjects	Dose	Duration	Summary of Safety
Rafrar et al. (2017)	Pomegranate (Punica Granatum L.) Peel Hydroalcoholic extract supplementation reduces pain and improves clinical symptoms of knee osteoarthritis: a randomized, double-blind placebo controlled study	Female subjects	500 mg of pomegranate peel extract	Two capsules daily for 8 weeks	No adverse effects were observed.

[Attachment II1083.2-VER.11-A1, II1083.2-VER.11-A2, II1083.2-VER.11-A3, II1083.2-VER.11-A4, II1083.2-VER.11-A5, II1083.2-VER.11-A6]

Question 2

FDA's question on the potential allergenicity of pomegranate extract has not been addressed adequately before. Hence, we have a follow up concern that needs to be clearly addressed.

Concern to be addressed on allergenicity:

(a) FDA has identified several published references that document allergic and anaphylaxis reactions to pomegranate (or its constituents). Please discuss why such publicly available information does not contradict your GRAS conclusion. Please make your response specific and targeted. In your response you may utilize to the following facts (in addition to the history of consumption): (I) pomegranate is not one of the major 9 allergens, (II) all foods including widely consumed foods may pose some allergenic risk to some people in the world, and (III) people who are allergic to specific foods are usually aware of it so they can avoid those foods.

(b) The current literature on the allergenicity of pomegranate shows that some of the allergy-eliciting constituents of pomegranate have been identified. Please provide a discussion on these allergy-eliciting constituents of pomegranate and justify why the presence of such allergy-eliciting substances in pomegranate and pomegranate extract does not invalidate your GRAS conclusion. Please make your response specific and targeted. Obviously, the response to this question will have some similarity to that of the previous question.

Response

(a) *Additional literature search on publicly available studies on the allergic and anaphylaxis reactions to pomegranate were performed. The studies that were identified in this literature search were specific to pomegranate fruit or pomegranate seed. Pomella pomegranate extract is made from pomegranate fruit that is further extracted. Pomegranate is not one of the 9 major Food Allergen*

Labeling and Consumer Protection Act (FALCPA) allergens. In addition, pomegranate has been historically consumed as a fruit. Gaig et al. (1999) mentions that pomegranate is widely consumed in certain areas of the world, particularly in Asia and Mediterranean countries during certain seasons. In the same publication, Gaig et al. refers to a few allergic reactions from patients who consumed pomegranate fruit or seeds, but also mentions that "patients with pomegranate allergy are often sensitized to other allergens" and very rarely solely resulting from pomegranate. Based on the information above, the publicly available information does not contradict the GRAS conclusion of Pomella pomegranate extract.

[Attachment II1083.2-VER.11-A7]

(b) *Although there have been cases of individuals having an allergic reaction after consuming pomegranate, the majority of the cases have been related to cross-reactivity with other allergens such as nuts and pollen. As stated previously, pomegranate is not one of the nine major FALCPA allergens. A few cases are summarized below:*

Four separate cases of allergic or anaphylactic reaction were studied regarding potential allergy-eliciting components of pomegranate. In one study by San Miguel et al. (2007), lipid transfer protein allergen (LTP) may have played a role in a patient who had an allergic reaction after consuming pomegranate. Skin prick tests (SPT) were "positive to Platanus acerifolia pollen, peach peel, and nuts" as well as serum tests with "high levels of IgE to Platanus acerifolia, peach, and walnut." The author stated that "pomegranate is an uncommon but potential allergen or severe systemic reactions." In another case by Petersen et al. (2011), a patient had an allergic reaction after consuming pomegranate. Again, SPT was performed and was positive "to mites, tree and grass pollen, ambrosia, mugwort, apple" and was also positive for pomegranate, more so on the seeds. Petersen et al. showed that the immunological tests had an IgE band at 9 kDA "identified as lipid transfer protein (LTP) which revealed a 77% sequence identity to the LTP from peach." In a third case studied by Enrique et al. (2006), the patient had a known allergy to hazelnut and peanuts. The SPT was "positive for grass, olive, plane tree, cypress, and chenopodium pollen, and for hazelnut, peanut, peach, apple, maize, and rice food extracts." The immunological test confirmed a peanut LTP in pomegranate owing that a "9-kDA binding band protein was also presented in other food extracts studied and in plane tree pollen extract." In the last allergic reaction case presented by Zhang et al. (2015), the patient with a known "tree-nut allergy" consumed pomegranate seeds. SPT was positive for pomegranate seed along with multiple tree nuts, but negative for pomegranate pulp. The immunological tests showed "sensitization to pine nut, cashew, pistachio, walnut (positive Jug r 1, negative Jug r 3), pecan, hazelnut (positive Cor a 9 and 14), and Brazil nut." Zhang et al. also mentioned that "reports of pomegranate allergy are rare and often linked to pollen/fruit cross-reactivity."

In other rare instances, other potentially allergy-eliciting constituents such as gibberellin regulated proteins and/or chitinase proteins are also known in pomegranates. However, based on information provided above and reviewed to date, these are thought to cause allergic reactions in very rare instances and most often, in conjunction with other more prominent known allergens (e.g. tree nuts, latex, and pollen, etc.).

Overall, these cases provide similar allergy-eliciting components of pomegranates, but with cross-reactivity with other allergens. Although, the cases presented had patients who consumed pomegranate fruit and/or pomegranate seed, Pomella pomegranate extract is made from pomegranate fruit that is further extracted. Therefore, the cases presented along the low frequency of pomegranate allergies, and the manufacture of Pomella pomegranate extract does not invalidate the GRAS conclusion.

[Attachment II1083.2-VER.11-A8, II1083.2-VER.11-A9, II1083.2-VER.11-A10, II1083.2-VER.11-A11]

Question 3

FDA's question on the ADME of punicalagin (the ellagitannin unique to pomegranate and abundant in the fruit husk) has not been addressed adequately before. Hence, we have a follow up concern that needs to be clearly addressed.

Concern to be addressed on the ADME of punicalagin:

Please briefly discuss the ADME of punicalagin and discuss if it is comparable to the ADME of other common dietary ellagitannins. Remember that the similarity of ADME profile of punicalagin with other dietary ellagitannins may support the safety of consumption of pomegranate-specific ellagitannin.

Response

According to literature detailing pomegranate ellagitannins (Heber 2011), the most abundant type of polyphenols in pomegranate, especially in pomegranate juice, are hydrolyzable tannins releasing ellagic acid on hydrolysis and subsequently forming urolithins such as Urolithin A. Punicalagin is an ellagitannin found specifically in pomegranate. Despite this exclusivity, punicalagin is another among many ellagitannins and is part of a family of phytochemicals, that includes tannins such as punicalin and gallagic acid. According to this publication, all of these ellagitannins have in common the ability to be hydrolyzed to ellagic acid.

The metabolism of ellagitannins in the gastrointestinal tract is complex (Silacci and Tretola 2019). The process remains the same regardless of the size of the ellagitannin molecule, hydrolysis in the stomach that forms ellagic acid followed by other decarboxylation reactions carried on by other microbiota in the colon. The differences in the composition of the microbiota from individual to individual contributes more to the conversion of the metabolites to urolithins than the differences in conversion of the larger ellagitannins from one another. The pomegranate ellagitannins are not absorbed intact into the blood stream but are hydrolyzed to ellagic acid over several hours in the intestine. Ellagitannins are also metabolized into urolithins by the gut microflora, which are conjugated in the liver and excreted in the urine.

In another study, the bioavailability of the ellagic acid was evaluated after consuming pomegranate extract (Gonzalez-Sarrias et al. 2015). The pomegranate extracts as part of this study contained either a high punicalagin to ellagic acid ratio or a low punicalagin to ellagic acid ratio. The authors concluded that there was a variability in the pharmacokinetics of ellagic acid, but confirms that "a higher free EA intake

does not enhance EA bioavailability, but the biological action in the gastrointestinal tract could be higher and also promotes the production of urolithins."

Food ellagitannins progress through the same metabolomic fate (Ortega Villalba et. al. 2019). This is well described across multiple botanicals, inclusive of pomegranate. The metabolic fate of Punicalagin is the same as for other common dietary ellagitannins. The compounds generated during the metabolic process are ellagic acid and urolithins. The consumption of ellagitannins, inclusive of punicalagin, results in the same generation of ellagic acid and urolithins. Therefore, the estimated daily intake based on the intended foods as specified in the GRAS notification for Pomella pomegranate extract includes ellagitannins, inclusive of punicalagin which all undergo the same metabolic fate.

[Attachment(s) II1083.2-VER.11-A12, II1083.2-VER.11-A13, II1083.2-VER.11-A14, II1083.2-VER-A15]

Question 4

FDA's question on your final safety evaluation was not accurately completed. Hence, we have a follow-up request that needs to be addressed.

Concern to be addressed on the accuracy of the stated 90th percentile EDI:

To complete your safety determination for exposure to whole fruit pomegranate extract, please compare your ADI (corrected ADI from 11/9/22 amendment version 3) to the appropriate 90th percentile EDI value and state your corresponding safety conclusion. Please refer to Chemistry question above (#3) on the appropriate approach to derive EDI exposure values.

Response

The updated cumulative EDI value for the Total Population at the 90th percentile based on the determination from Crème Global software is 95 mg/day.

Based on this newly determined cumulative EDI, the EDI is still below the ADI of 360 mg/day. Therefore, it can be concluded that the ingredient, Pomella pomengranate extract, is reasonably expected to be safe.

ADDITIONAL ITEMS FOR CLARIFICATION (RECEIVED 3/24/23)

Question 1

In the amendment dated 10/7/2022, we note that the specification for Salmonella was revised as "Absent/10 g" whereas the results were reported as "Absent/25 g" or "Absent" (see Attachment II1083.2-VER.8-A1). Please clarify the specification limit for Salmonella.

Response

For clarification, the specification for Salmonella is Absent/25g.

Question 2

In the 10/7/2022 amendment, you explained why the risk of pesticides being present in the pomegranate fruit extract is negligible, indicating that there is no justification for proposing the pesticide limit. Please provide a statement that the pesticide residues are not expected to be present in the final ingredient and therefore that the pesticide residue limit is no longer part of the specifications for the pomegranate fruit extract in the Table 2 (p. 10).

Response

In Progress

Additional information has been requested to the Sponsor. The response to this question will be addressed in the follow-up response.

Question 3

In the 10/28/2022 amendment, we note that the dietary exposure to pomegranate fruit extract was provided for each food category separately (Tables 1-4, pp. 3-6). We also note that the dietary exposure from all intended uses of pomegranate fruit extract was estimated by simply summing the exposure estimates for the individual food categories. We do not consider this approach appropriate because the population consuming each food category is probably not the same. The dietary exposure to the pomegranate fruit extract from the intended uses should be estimated based on a subset of the NHANES food codes representing all proposed food categories, not estimated separately for individual subsets of the NHANES food codes, each representing a different proposed food category.

- Please revise the dietary exposure to pomegranate fruit extract and provide mean and 90th percentile eaters-only dietary exposures for the U.S. population 2 years and older based on a subset of the NHANES food codes representing all proposed food categories combined with the corresponding use levels of the extract in those food categories. Please consult FDA's Guidance for Industry: Estimating Dietary Intake of Substances in Food for guidance on how to perform the dietary exposure assessment.

- In the 10/28/2022 amendment, we note that in your dietary exposure estimate for pomegranate polyphenols (Table 5, p.6), you applied 88.83% polyphenols instead of the proposed specification limit of 50% polyphenols. Please clarify the maximum level of polyphenols in the pomegranate fruit extract.

With regard to your response #7, we consider that you did not address the cumulative dietary exposure to pomegranate polyphenols (from background sources and the intended uses of pomegranate fruit extract) for the U.S. population aged 2 years and older at the mean and 90th percentile. Please discuss the cumulative dietary exposure to pomegranate polyphenols and the impact of the proposed uses of the pomegranate fruit extract on the current dietary exposure to the polyphenols for the U.S. population.

Response

Further evaluation and determination of the dietary exposure of the pomegranate fruit extract in the three intended foods (dairy products, juices, chocolate candies) as well as the existing food (pomegranate/pomegranate juice) was performed through the Crème Global software. The following parameters were used for this determination:

1. *Owing to the 50 mg/serving of the ingredient, the concentrations of pomegranate fruit extract in each of the intended foods were calculated based on RACC serving size or ERS serving size. The concentration of pomegranate fruit extract in pomegranate was calculated based on one serving of pomegranate fruit extract is equivalent to 2-3 fl oz. of pomegranate. Therefore, the levels of pomegranate fruit extract are determined by dividing 1 serving of pomegranate fruit extract (50 mg/serving) by 3 fl oz (i.e. 16.7 mg/serving).*

Food	Levels of Pomella (mg/serving)	Serving size	Concentration of Pomella (mcg/g)
Dairy milk	50	244	204.9180328
Chocolate candies	50	30	1666.666667
Juices	50	187	267.3796791
Pomegranate/Pomegranate Juice	16.7	187	89.12655971

2. *The determination of the dietary exposure of pomegranate fruit extract in all Foods (intended foods and existing foods) at the total population, not including breast-feeding infants, is based on the 90th percentile consumption. In addition, the mean dietary exposure of the pomegranate fruit extract in all Foods was also determined.*

Cumulative EDI for Pomella in All Foods in the Total Population

Population Group	Age Group	Eaters only (mg/day)	
		Mean	90th Percentile
Total Population	2 years old to Adults	41	95

The specification for polyphenols remains at NLT 50.00%. However, as a conservative approach and to provide a conservative estimation, 88.83% was a reported result from one the production lots and was used for the calculation for the estimated daily intake of the total polyphenols. This met the specification for total polyphenols.

Based on the conservative approach of the 88.83% result of total polyphenols, 90th percentile of the total population of the eaters only group of Pomella pomegranate extract at all Foods, the cumulative dietary exposure of the pomegranate polyphenols is 84.39 mg/day. This cumulative dietary exposure, owing to the NHANES consumption data, assumes that the intended food categories consumed contain the

maximum quantity of pomegranate fruit extract, which could lead to an overestimation of the intended levels on the consumption of pomegranate fruit extract among consumers of the intended foods.

Conclusion

We sincerely appreciate this opportunity to clarify the additional questions submitted so far as part of this review and we look forward to a positive assessment of these responses and the notification itself. Should the agency have any additional questions or requests on the above responses or the prior responses, please let us know at your earliest convenience and we will do everything we can to address those promptly. We are targeting to provide the remainder of responses requested on or before Friday April 28th, 2023.

Attachments

II1083.2-VER.11-A1	Paller CJ, Ye X, Wozniak PJ, Gillespie BK, Sieber PR, Greengold RH, Stockton BR, Hertzman BL, Efros MD, Roper RP, Liker HR, Carducci MA. A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer. *Prostate Cancer Prostatic Dis.* 2013 March; 16(1): 50-55.
II1083.2-VER.11-A2	Adel-Mehraban MS, Tansaz M, Mohammadi M, Yavari M (2022). Effects of pomegranate supplement on menopausal symptoms and quality of life in menopausal women: A double-blind randomized placebo-controlled trial. *Complementary Therapies in Clinical Practice* 46 (2022) 101544.
II1083.2-VER.11-A3	Pantuck AJ, Pettaway CA, Dreicer R, Corman J, Katz A, Ho A, Aronzon W, Clark W, Simmons G, Heber D (2015). A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer. *Prostate Cancer and Prostatic Disease* (2015) 18, 242-248.
II1083.2-VER.11-A4	Dormal V, Pachikian B, Debock E, Buchet M, Copine S, Deldicque (2022). Evaluation of a dietary supplementation combining protein and a pomegranate extract in older people: a safety study. *Nutrients*. 2022 Dec 6;14(23):5182.
II1083.2-VER.11-A5	Mirmiran P, Fazeli MR, Asghari G, Shariee A, Azizi F (2010). Effect of pomegranate seed oil on hyperlipidaemic subjects: a double-blind placebo-controlled clinical trial. *British Journal of Nutrition* (2010), 104, 402-406.
II1083.2-VER.11-A6	Rafraf M, Hemmati S, Jafarabadi MA, Moghaddam A Haghighhian MK (2017). Pomegranate (Punica Granatum L.) Peel Hydroalcoholic extract supplementation reduces pain and improves clinical symptoms of knee osteoarthritis: a randomized, double-blind placebo controlled

	study. *Iran Red Crescent Med J.* 2017 January; 19(1):e385
II1083.2-VER.11-A7	Gaig P, Bartolome B, Lleonart R, Garcia-Ortega P, Palacios R, Richart C (1999). Allergy to pomegranate (Punica granatum). *Allergy* 1999: 54:287-296.
II1083.2-VER.11-A8	San Miguel-Moncin M, Lombardero M, Barber D, Enrique E, Alonso R, Basagana M, Cistero-Bahima A (2007). Identification of an allergenic lipid transfer protein in pomegranate-induced anaphylaxis. *J Allergy Clin Immunol* Volume 119, Number 1.
II1083.2-VER.11-A9	Petersen A, Kleinheinz A, Jappe U (2011). Anaphylactic reactions to pomegranate: identification and characterization of eliciting IgE-reactive components. *Clinical and Translational Allergy* 2011. 1(Supp 1): P88.
II1083.2-VER.11-A10	Zhang S, Baker M. Pomegranate seed allergy in a tree-nut allergic child. *Medically Challenging Cases/Ann Allergy Asthma Immunol* 127 (2021) S58-S129.
II1083.2-VER.11-A11	Enrique E, Utz M, De Mateo JA, Castello JV, Malek T, Pineda F (2006). Allergy to lipid transfer proteins: cross-reactivity among pomegranate, hazelnut, and peanut. *Annals of Allergy, Asthma & Immunology* Volume 96, January 2006 122-123.
II1083.2-VER.11-A12	Heber D (2011). Herbal Medicine: Biomolecular and Clinical Aspects. 2nd Edition, Boca Raton, FL: CRC Press/Taylor & Francis.
II1083.2-VER.11-A13	Silacci P and Tretola M (2019). Pomegranate's Ellagitannins: Metabolism and Mechanisms of Health Promoting Properties. *Nutrition & Food Science International Journal* Vol 9, Issue 4; October 2019.
II1083.2-VER.11-A14	Gonzalez-Sarrias A, Garcia-Villalba R, Nunez-Sanchez MA, Tome-Carneiro J, Zafrilla P, Mulero J, Tomas-Barberan FA, Espin JC (2015). Identifying the limits for ellagic acid bioavailability: a crossover pharmacokinetic study in healthy

	volunteers after consumption of pomegranate extracts. *Journal of Functional Foods* 19 (2015) 225-235.
II1083.2-VER.11-A15	Ortega Villalba KJ, Barka FV, Velez Pasos C, Rodriguez PE (2019). Food Ellagitannins: Structure, Metabolomic Fate, and Biological Properties. Tannins – Structural Properties, Biological Properties and Current Knowledge. IntechOpen 2019.

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4/28/2023

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RE: Second Response to GRN 1064 Pomegranate Extract – Toxicology-Related Question
II1083.2-VER.12

Dear Dr. DiFranco,

This is a second response following the prior response issued on 4/19/23 to address the remaining question from the FDA questions/comments with respect to GRN 001064. In addition, owing to the feedback received during the meeting with FDA on 4/25/23, clarification on the dietary exposure of the ingredient and the polyphenols was re-evaluated in the intended food categories and is summarized in this report.

Should you have any questions or concerns with this additional information or have additional requests based on the information provided so far, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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TOXICOLOGY-RELATED QUESTIONS (RECEIVED 3/8/23)

Question 4

FDA's question on your final safety evaluation was not accurately completed. Hence, we have a follow-up request that needs to be addressed.

Concern to be addressed on the accuracy of the stated 90th percentile EDI:

To complete your safety determination for exposure to whole fruit pomegranate extract, please compare your ADI (corrected ADI from 11/9/22 amendment version 3) to the appropriate 90th percentile EDI value and state your corresponding safety conclusion. Please refer to Chemistry question above (#3) on the appropriate approach to derive EDI exposure values.

Response

The updated cumulative EDI value for the total population at the 90th percentile for the intended foods of chocolate candies, dairy milk, and juices is 96 mg/day. For additional information regarding this determination, refer to the response to Question 3 below for Additional Items for Clarification (Received 3/24/23).

Based on this newly determined cumulative EDI, the EDI is still below the ADI of 360 mg/day. Therefore, it can be concluded that the ingredient, Pomegranate fruit extract, is reasonably expected to be safe.

ADDITIONAL ITEMS FOR CLARIFICATION (RECEIVED 3/24/23)

Question 2

In the 10/7/2022 amendment, you explained why the risk of pesticides being present in the pomegranate fruit extract is negligible, indicating that there is no justification for proposing the pesticide limit. Please provide a statement that the pesticide residues are not expected to be present in the final ingredient and therefore that the pesticide residue limit is no longer part of the specifications for the pomegranate fruit extract in the Table 2 (p. 10).

Response

Verdure Sciences has confirmed that pesticides are not used during harvest and post-harvest of the pomegranate fruit nor is grown adjacent to any other crops using pesticides. Moreover, the pomegranate fruit is washed with water to remove dust and debris of any kind prior to further processing. Owing to crop management control processes that are implemented, Verdure Sciences does not expect pesticide residues to be present in the finished ingredient, and therefore, pesticide residue limit is not included as part of the specifications for the finished ingredient, pomegranate fruit extract.

Question 3

In the 10/28/2022 amendment, we note that the dietary exposure to pomegranate fruit extract was provided for each food category separately (Tables 1-4, pp. 3-6). We also note that the dietary exposure

from all intended uses of pomegranate fruit extract was estimated by simply summing the exposure estimates for the individual food categories. We do not consider this approach appropriate because the population consuming each food category is probably not the same. The dietary exposure to the pomegranate fruit extract from the intended uses should be estimated based on a subset of the NHANES food codes representing all proposed food categories, not estimated separately for individual subsets of the NHANES food codes, each representing a different proposed food category.

- Please revise the dietary exposure to pomegranate fruit extract and provide mean and 90th percentile eaters-only dietary exposures for the U.S. population 2 years and older based on a subset of the NHANES food codes representing all proposed food categories combined with the corresponding use levels of the extract in those food categories. Please consult FDA's Guidance for Industry: Estimating Dietary Intake of Substances in Food for guidance on how to perform the dietary exposure assessment.

- In the 10/28/2022 amendment, we note that in your dietary exposure estimate for pomegranate polyphenols (Table 5, p.6), you applied 88.83% polyphenols instead of the proposed specification limit of 50% polyphenols. Please clarify the maximum level of polyphenols in the pomegranate fruit extract.

With regard to your response #7, we consider that you did not address the cumulative dietary exposure to pomegranate polyphenols (from background sources and the intended uses of pomegranate fruit extract) for the U.S. population aged 2 years and older at the mean and 90th percentile. Please discuss the cumulative dietary exposure to pomegranate polyphenols and the impact of the proposed uses of the pomegranate fruit extract on the current dietary exposure to the polyphenols for the U.S. population.

Response

Based on the feedback received during the FDA meeting held on 4/25/23, the dietary exposure of the pomegranate fruit extract was re-evaluated using the combined dietary exposure in the three intended foods only (chocolate candies, dairy milk, and juices).

The following parameters were used for this determination:

1. *Owing to the 50 mg/serving of the ingredient, the concentrations of pomegranate fruit extract in each of the intended foods were calculated based on RACC serving size or ERS serving size. This information is captured below here in Table 1.*

Table 1 – Concentration of Pomegranate Fruit Extract in each Intended Food

Intended Food	Levels of Pomegranate Fruit Extract (mg/serving)	Serving size	Concentration of Pomegranate Fruit Extract (mcg/g)
Dairy milk	50	244	204.9180328
Chocolate candies	50	30	1666.666667
Juices	50	187	267.3796791

2. *The determination of the dietary exposure of pomegranate fruit extract in only the intended food categories at the total population, not including breast-feeding infants, is based on the 90th percentile consumption. In addition, the mean dietary exposure of the pomegranate fruit extract in the intended food categories was also determined. The Cumulative EDI for Pomegranate Fruit Extract in all intended food categories in the Total Population is defined in Table 2 here below.*

Table 2 – Cumulative EDI of all intended foods

Population Group	**Age Group**	**Eaters only (mg/day)**	
		Mean	90th Percentile
Total Population	2 years old to adults	41	96

Additional FDA feedback regarding the dietary exposure of the total pomegranate polyphenols in comparison to other foods containing pomegranate polyphenols was provided from the FDA meeting on 4/25/23. A conservative approach of the 88.83% of total polyphenols test result delivers a dietary exposure of the total pomegranate polyphenols at the 90th percentile equal to 85.28 mg/day owing to the 90th percentile of the total population of the eaters only group of Pomegranate fruit extract, in all intended foods (chocolate candies, dairy milk, and juices). This total pomegranate polyphenols dietary exposure in the intended uses in chocolate candies, dairy milk, and juices is negligible relative to the total pomegranate polyphenols dietary exposure from other foods containing the pomegranate polyphenols.

CONCLUSION

We sincerely appreciate this opportunity to clarify the additional questions submitted so far as part of this review and for the Agency to address our questions in the recent FDA meeting held on 4/25/23. Overall, we look forward to a positive assessment of these responses and the notification itself.

Should the agency have any additional questions or requests, please let us know at your earliest convenience and we will do everything we can to address those promptly.

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stephen.difranco@fda.hhs.gov

RE: Response to GRN 1064 Pomegranate Extract – Email dated on 5/26/23
II1083.2-VER.13

Dear Dr. DiFranco,

This is a response to the email on 5/26/23 to address the remaining issue from FDA with respect to GRN 001064. This to clarify the dietary exposure of the ingredient in the intended food categories with the appropriate consumer population.

Should you have any questions or concerns with this additional information or have additional requests based on the information provided so far, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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EMAIL DATED ON 5/26/23

Issue

In reviewing the latest amendment we identified a remaining issue regarding the exposure estimate. Please respond to the below from our review chemist;

> In the amendment dated April 28, 2023 (page 5), you estimated the dietary exposure to pomegranate extract from the intended uses to be 41 mg/p/d at the mean and 96 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older. In addition, in the amendment dated April 19, 2023 (page 10), you estimated the cumulative dietary exposure to pomegranate extract to be 41 mg/p/d at the mean and 95 mg/p/d at the 90th percentile. You also indicated that the above-mentioned estimates were for the "eaters-only" population.
>
> However, we note that your dietary exposure estimates are for the "total population", which includes the non-eaters and eaters. Please provide the dietary exposure estimates for the **eaters-only** population, including the cumulative dietary exposure to pomegranate extract (dairy milk, chocolate candies, juices, raw pomegranate, and pomegranate juice) as well as the dietary exposure from the intended uses (dairy milk, chocolate candies, and juices). We note that to estimate dietary exposure for the eaters-only population the "**consumer exposure**" option, not the "total population" option, should be selected in the calculations and outputs in the Crème Global software.

Response

We acknowledge the confusion of the term "total population." The dietary exposure estimates presented in the amendments dated April 19, 2023 and April 28, 2023 was inappropriately identified as Total Population and should be identified as the Total Consumer Exposure Population (i.e., eaters-only population).

In re-evaluation of the dietary exposure analysis from the Crème Global software, the combined dietary exposure of the pomegranate fruit extract in the three intended foods (chocolate candies, dairy milk, and juices) and in raw pomegranate/pomegranate juice and in the total consumer exposure population, not including breast-feeding infants, at the 90th percentile is confirmed as 95 mg/day. The mean dietary exposure of the pomegranate fruit extract in the three intended foods (chocolate candies, dairy milk, and juices) and in raw pomegranate/pomegranate juice and in the total consumer exposure population, not including breast-feeding infants, is confirmed as 41 mg/day. Below is a screenshot of the Crème Global Analysis which presents the dietary exposure under the column "Consumer Exposure."

exposure_type	Group Code	Group Name	Statistic	stratifier	Calculation Type	Consumer Exposure	Total Population Exposure	Units
Pomella	Dairy, Chocolate Candies, Juice, Pomegranate	Dairy, Chocolate Candies, Juice, Pomegranate	mean	Total Population	Absolute	41322.8161	27821.76548	ug/day
Pomella	Dairy, Chocolate Candies, Juice, Pomegranate	Dairy, Chocolate Candies, Juice, Pomegranate	P90.0	Total Population	Absolute	95835.35068	77082.99219	ug/day

In re-evaluation of the dietary exposure analysis from the Crème Global software, the combined dietary exposure of the pomegranate fruit extract in the three intended foods only (chocolate candies, dairy milk, and juices) and in the total consumer exposure population, not including breast-feeding infants, at the 90th percentile is confirmed as 96 mg/day. The mean dietary exposure of the pomegranate fruit extract in the

three intended foods only (chocolate candies, dairy milk, and juices) and in the total consumer exposure population, not including breast-feeding infants, is confirmed as 41 mg/day. Below is a screenshot of the Crème Global Analysis which presents the dietary exposure under the column for "Consumer Exposure."

exposure_type	Group Code	Group Name	Statistic	stratifier	Calculation Type	Consumer Exposure	Total Population Exposure	Units
Pomella	Chocolate Candies, Dairy, juice	Chocolate Candies, Dairy, juice	mean	Total Population	Absolute	41468.35221	27765.23418	ug/day
Pomella	Chocolate Candies, Dairy, juice	Chocolate Candies, Dairy, juice	P90.0	Total Population	Absolute	96165.78399	77082.99219	ug/day

CONCLUSION

We sincerely appreciate this opportunity to clarify the remaining concern submitted as part of this review. Overall, we look forward to a positive assessment of these responses and the notification itself.

Should the agency have any additional questions, please let us know at your earliest convenience and we will do everything we can to address those promptly.

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7/28/2023

Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
United States Food and Drug Administration
stephen.difranco@fda.hhs.gov

RE: Response to GRN 1064 Pomegranate Extract – Email dated on 7/21/23
II1083.2-VER.14

Dear Dr. DiFranco,

This is a response to the email dated 7/21/23 to address additional questions from FDA with respect to GRN 001064.

Should you have any questions or concerns with this additional information, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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QUESTIONS EMAILED ON 7/21/23

Question 1

1. In the specification in Table 2 (p. 10, GRN 1064), you proposed not less than 50% of polyphenols (≥ 50%). Please clarify whether the parameter for polyphenols (≥ 50%) represents the content of polyphenols other than punicalagins or it represents the content of total polyphenols including punicalagins.

Response

The parameter for polyphenols (≥ 50%) represents the content of total polyphenols including punicalagins.

Question 2

2. According to the supplier's Certificate of Analysis (II1083.2-VER.8, 10/7/2022 amendment), there are separated specifications for punicalagins (≥ 30%) and polyphenols (≥ 50%) with conforming test results. However, we note that Table 2 (p. 10) does not include the specification for punicalagins. Please confirm that you proposed the specification limit only for polyphenols (≥ 50%), but not for punicalagins (≥ 30%), as presented in Table 2 (p.10). If the specification parameter for "polyphenols" in Table 2 (p. 10) does not represent polyphenols including punicalagins (see question 1 above), please include a separate specification parameter for the punicalagin content.

Response

For this ingredient, the proposed specification limit is only for polyphenols (≥ 50%) as presented in Table 2 (p. 10). Punicalagins is a subset of polyphenols and, therefore, the total polyphenol content is inclusive of punicalagins.

Question 3

3. According to the 10/28/22 amendment (II1083.2-VER.10, p.6) , you note that "Based on the test results using the highest total polyphenols and punicalagin in one of the COAs (88.83%), the estimated daily intake of total polyphenols for each of the proposed food is shown in Table 5." Please clarify whether the value of 88.83% for "total polyphenols and punicalagin" is the sum of polyphenols and punicalagin. We note that according to the Certificate of Analysis (II1083.2-VER.8, 10/7/2022 amendment), the highest result is 88.31% (31.67% punicalagins + 56.64% polyphenols), not 88.83%. Please clarify how you calculated the value of 88.83%.

Response

Owing to the inclusion of punicalagins in the total polyphenol content, the value presented in the 10/28/22 amendment (II1083.2-VER.10, p. 6) has been corrected for the highest total polyphenol content. Therefore, as a clarification, the highest total polyphenol content in the COAs, as presented in the 10/07/2022 amendment (Lot number: LPR1EP1913K03), is corrected to 57.36% polyphenols.

Question 4

4. According to Table 1 titled "Proximate Analysis of Pomella®" in (p. 8, GRN 1064), Pomella® contains 90.79% carbohydrate (by difference). We note that according to the specification in Table 1 (p. 10), the pomegranate fruit extract contains ≥ 50% polyphenols and as such the carbohydrate content cannot be 90.79%. Therefore, we do not consider that Table 1 is representing the proximate analysis of pomegranate fruit extract. Please confirm that the data in Table 1 does not represent the proximate analysis of pomegranate fruit extract and provide the correct data if available, or provide a discussion to support the proximate analysis in Table 1.

Response

Polyphenols are included in the total carbohydrate content calculations, which make up approximately or no less than (NLT) 50% of the total 90.79% carbohydrates (by difference) in Table 1 for the Proximate Analysis values reported. The Polyphenol specification in Table 2, p 10 identifies the amount that is being controlled as part of the quality practice to ensure consistency of the finished ingredient.

Question 5

5. Please state that pomegranate fruit extract is manufactured in accordance with current good manufacturing practices (cGMP) and that all processing aids are food-grade and are used in accordance with appropriate U.S. regulations, are GRAS for their respective uses, or are the subject of an effective food contact notification.

Response

The pomegranate fruit extract, Pomella®, is manufactured in accordance with current good manufacturing practices and all processing aids used in the manufacturing of this ingredient are food-grade and are used in accordance with the appropriate U.S. regulations.

CONCLUSION

We sincerely appreciate this opportunity to clarify the remaining questions submitted as part of this review. Overall, we look forward to a positive assessment of these responses and the notification itself.

Should the agency have any additional questions, please let us know at your earliest convenience and we will do everything we can to address those promptly.

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7/31/2023

Stephen DiFranco, PhD
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stephen.difranco@fda.hhs.gov

RE: Expanded Response to GRN 1064 Pomegranate Extract – Email dated on 7/21/23
II1083.2-VER.14.1

Dear Dr. DiFranco,

This is an expansion to the response submitted specifically for Question 4 dated 7/28/23 (II1083.2-VER.14) in regards to your email request dated 7/21/23 for GRN 1064.

Should you have any questions or concerns with this additional information, please let us know, and we'll be sure to address that promptly for the Agency.

Sincerely,

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

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EXPANDED RESPONSE TO QUESTION 4

Question 4

4. According to Table 1 titled "Proximate Analysis of Pomella®" in (p. 8, GRN 1064), Pomella® contains 90.79% carbohydrate (by difference). We note that according to the specification in Table 1 (p. 10), the pomegranate fruit extract contains ≥ 50% polyphenols and as such the carbohydrate content cannot be 90.79%. Therefore, we do not consider that Table 1 is representing the proximate analysis of pomegranate fruit extract. Please confirm that the data in Table 1 does not represent the proximate analysis of pomegranate fruit extract and provide the correct data if available, or provide a discussion to support the proximate analysis in Table 1.

Response

Polyphenols are included in the total carbohydrate content calculations, which make up approximately or no less than (NLT) 50% of the total 90.79% carbohydrates (by difference) in Table 1 for the Proximate Analysis values reported. The Polyphenol specification in Table 2, p 10 identifies the amount that is being controlled as part of the quality practice to ensure consistency of the finished ingredient.

As an expansion to the above response issued on 7/28/23 (II1083.2-VER.14), there are known interactions between polyphenols and carbohydrates forming a cohesive matrix not otherwise distinguishable in how the Proximate Analysis testing itself is conducted, and more specifically how the Carbohydrate value is calculated therefrom. According to Jakobek (2015), "the reason for these interactions could be the formation of weak bonds (H-bonds and hydrophobic interaction) between polyphenols and cell wall components. Hydrogen bonds are formed between hydroxyl groups of polyphenols and oxygen atoms of the glycosidic linkages of polysaccharides." This information provides additional evidence that the polyphenols present in the Pomegranate Extract should be included in the total carbohydrate content in support with the original Proximate Analysis for Pomella®, as presented in Table 1, page 8, which still allows for the Polyphenols value in the Specifications from Table 2, page 10 to be assayed as part of the routine quality control practices for the finished ingredient.

Attachment: II1083.2-VER.14.1-A1

CONCLUSION

We sincerely appreciate this opportunity to expand on the response to Question 4 submitted as part of this review. Overall, we look forward to a positive assessment of these responses and the notification itself.

Should the agency have any additional questions, please let us know at your earliest convenience and we will do everything we can to address those promptly.

ATTACHMENT

II1083.2-VER.14.1-A1	Jakobek L (2015). Interactions of polyphenols with carbohydrates, lipids, and proteins. *Food Chemistry* 175 (2015) 556-567.

The attachment has been removed in accordance with copyright laws. The removed reference citation can be found in the prior attachment list.

From: Joel Villareal
To: DiFranco, Stephen
Cc: Jim Lassiter; Brandon M. Griffin; Kenneth Cairns; Kent Phan; Livia Consedine
Subject: Re: [EXTERNAL] Re: GRN 1064 Pomegranate Extract Items for clarification
Date: Wednesday, August 9, 2023 3:53:20 PM
Attachments: image001.png

Dear Dr. DiFranco,

Thank you for your email. We would like to respectfully respond to the two questions below and confirm the estimated dietary exposure to pomegranate polyphenols.

1. Please confirm that, based on the highest total polyphenol content of 57.36%, an estimate of dietary exposure for the U.S. population aged 2 years and older to polyphenols from the intended uses of pomegranate extract is expected to be 55.1 mg/p/d (96 mg/p/d x 57.36%) at the 90th percentile.

   Response: Yes. We confirm that the estimated dietary exposure for the U.S. population aged 2 years and older to polyphenols from the intended uses of pomegranate extract is 55.1 mg/p/d at the 90th percentile.

2. In addition, please confirm that the cumulative dietary exposure to pomegranate polyphenols from the intended uses of pomegranate fruit extract and the background sources (pomegranate and pomegranate juices) is expected to be 54.5 mg/p/d (95 mg/p/d x 57.36%) at the 90th percentile.

   Response: Yes. We confirm that the estimated dietary exposure to pomegranate polyphenols from the intended uses of pomegranate fruit extract and the background sources (pomegranate and pomegranate juices) is 54.5 mg/p/d at the 90th percentile.

If there are any questions regarding this response, please let us know and we will be sure to address that promptly.

Sincerely,

Joel Villareal | Regulatory Director
Quality Development Services
joel@rejimus.com

signature_1575762594

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From: DiFranco, Stephen <Stephen.DiFranco@fda.hhs.gov>
Date: Wednesday, August 9, 2023 at 9:56 AM
To: Joel Villareal <joel@rejimus.com>
Subject: RE: [EXTERNAL] Re: GRN 1064 Pomegranate Extract Items for clarification

Hello Joel,

Just a quick follow up I received from our chemists regarding GRN 1064—we just need you to confirm our understanding of the following change noted in the last amendment:

> In the amendment dated 7/28/2023, the notifier stated that based on the certificates of analysis (COAs) provided in the 10/7/2022 amendment the highest total polyphenol (including punicalagins) content is 57.36%, and not 88.83% as stated in the 10/28/2022 amendment. We note that the notifier did not provide an updated estimate of dietary exposure to pomegranate polyphenols.
>
> 1. Please confirm that, based on the highest total polyphenol content of 57.36%, an estimate of dietary exposure for the U.S. population aged 2 years and older to polyphenols from the intended uses of pomegranate extract is expected to be 55.1 mg/p/d (96 mg/p/d x 57.36%) at the 90th percentile.
>
> 2. In addition, please confirm that the cumulative dietary exposure to pomegranate polyphenols from the intended uses of pomegranate fruit extract and the background sources (pomegranate and pomegranate juices) is expected to be 54.5 mg/p/d (95 mg/p/d x 57.36%) at the 90th percentile.

I had a chat with them regarding the above and it seems they are looking for a simple yes or no to complete the official record, as a GRN is the notifier's conclusion not FDA's.

Thanks,

Steve

Stephen DiFranco, PhD
Regulatory Review Scientist/Chemist

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients
U.S. Food and Drug Administration
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