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Generally Recognized as Safe (GRAS) Determination for the Use of AppleActiv DAPP™/Leahy DAPP™ (Dried Apple Peel Powder) in Conventional Foods

#805

Submitted By:
Leahy Orchards Inc.
Franklin, Quebec, Canada

Prepared For:
United States Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
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Generally Recognized as Safe (GRAS) Determination for the Use of AppleActiv DAPP™/Leahy DAPP™ (Dried Apple Peel Powder) in Conventional Foods

Part 1 – Signed Statements and Certification

GRAS Notice Submission:

Leahy Orchards Inc., of Franklin, Quebec, Canada ("Leahy") submits this GRAS notification in accordance with the requirements of 21 C.F.R. Part 170, Subpart E.

Name and Address:

Leahy Orchards Inc.
1772 Route 209
Franklin, Quebec, Canada
J0S 1E0

Name of the Notified Substance:

The notified substance is Dried Apple Peel Powder (DAPP) which is isolated from the peels of *Malus domestica* (Apples). The substance is also known commercially as AppleActiv DAPP™ and/or Leahy DAPP™.

Intended Conditions of Use of the Notified Substance:

Intended applications of use as a food ingredient for organic dried apple peel powder (DAPP) from *Malus domestica* include but are not limited to the following:

- Beverages, including fruit and/or vegetable juice products;
- Fortified foods and beverages;
- Milk and milk products;
- Bakery products;
- Dairy products and substitutes;
- Ready-to-eat cereals, sauces, dips, gravies and condiments.

These food categories were identified in the United States Department of Agriculture's (USDA) *Continuing Survey of Food Intakes by Individuals* (1994 – 1996 CFSII) or 21 C.F.R. 101.12, *Reference Amounts Customarily Consumed per Eating Occasion*. The estimated daily intake values for AppleActiv™/Leahy DAPP™ were based on regular consumption patterns of these food categories. The proposed food uses and the percent use level of AppleActiv™/Leahy DAPP™ are summarized below in *Table 1*:

***Table 1* – Summary of the Individual Proposed Uses and Use Levels of AppleActiv™/Leahy DAPP™ in the United States.**

Food Category	Proposed Food Uses	Use Level (%)
Fruits and fruit juices	Applesauce and cooked apples, fruit puree, fruit-based meal replacement drinks	0.8 – 1.6
Vegetables juices	Vegetable-based meal replacement drink	0.4 – 0.8
Milk and Milk Products	Yogurt	0.4 – 0.9
	Ice cream and milk	1.2 – 3.0
Bakery Products	Nutritional bars (e.g. breakfast, granola, meal-replacement, chocolate bars, gluten-free, superfood)	2.5 – 5.0
	Cake (all kinds of cakes and cupcakes, except coffeecakes and cheesecakes)	0.9 – 1.8
	Cookies (all varieties of cookies including sweet crackers such as graham cracker, except brownies)	10.0 – 20.0
	Pies (cobblers, fruit crisps, turnovers, other pastries)	0.8 – 1.6
	Pancakes and waffles	2.5 – 5.0
	Quickbreads and muffins (e.g. cornbread, fruit breads, pumpkin breads, zucchini breads, non-yeast coffee cakes and all kinds of muffins)	1.8 – 3.6
Dairy Products and Substitutes	Milk, milk-based drinks (e.g. instant breakfast, meal replacement, cocoa)	0.3 – 0.7
Ready-to-Eat Cereal	Cereals, granola clusters	2.0 – 3.9
Sauces, Dips, Gravies and Condiments	Major condiments (e.g. catsup, steak sauce, soy sauce, vinegar, teriyaki sauce, marinades)	0.1

Statutory Basis for Conclusion of GRAS Status:

AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder) has been determined to be GRAS through scientific procedures in accordance with 21 C.F.R. § 170.30(a) and (b).

Pre-Market Exempt Status:

AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder) is not subject to the premarket approval requirements of the Federal Food, Drug and Cosmetic Act based on the conclusion that the notified substance is GRAS under the conditions of intended use.

Data Availability:

The data and information that serve as the basis for the conclusion that AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder) is GRAS for its intended use, will be made available to the FDA upon request. At the FDA's option, a complete copy of the information will be sent to FDA in either paper or electronic format upon request to Leahy Orchards Inc. or the information will be available for review at Leahy Orchards Inc. located at 1772 Route 209, Franklin, Quebec, Canada during normal business hours.

Freedom of Information Act Statement:

None of the information in this GRAS notice is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

Certification:

To the best of our knowledge, we certify that 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 AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder).

FSIS Statement:

Not applicable.

Name, Position and Signature of Notifier:

X (b) (6) Date: July 26,2018

Lorraine Leahy, RHN
Director, Division of Functional Foods
Leahy Orchards Inc.

Part 2 – Identity, Method of Manufacture, Specifications and Physical or Technical Effect

2.1 – Identity of the GRAS Substance

The subject of this Generally Recognized as Safe (GRAS) determination is the peels of various cultivars of *Malus domestica*. The finished product is known commercially as AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder).

2.2 – Source of the GRAS Substance

AppleActiv™/Leahy DAPP™ is made from 100% organic dried apple peels that are sourced solely from orchard apples (*Malus domestica*) that are grown in North America (CAS#: 89957-48-2). The final product is a light to dark beige powder. AppleActiv™/Leahy DAPP™ contains only apple peels from growers committed to using certified organic processes and that have obtained USDA Organic/EcoCert Organic certification (please see attached a copy of the Organic Certificate in Appendix 1).

There are over 7,500 cultivars of apples. Leahy Orchards uses apple peels from several different *Malus domestica* cultivars. These cultivars are as follows:

- Cortland
- Delicious
- Empire
- Macintosh
- Spy
- Greening
- Rome
- Ida Red
- Liberty
- Macoun
- Mix
- Paula Red
- Romes
- Spartan

To a lesser extent, the following *Malus domestica* cultivars are also used:

- Gala
- Jonadel
- Lobo
- Melba

2.3 – Description of the GRAS Substance

The GRAS substance of this notification is AppleActiv™/Leahy DAPP™, which is a powder of dried apple peels from organic apples. Research shows that the peel of the apple contains a much higher concentration of phenolic compounds compared to the flesh and other edible parts of the apple (Wolfe et al., 2003; Podsedek et al., 2000; Liu et al., 2001; Burda et al., 1990; Escarpa and Gonzalez, 1998; Ju et al., 1996). Therefore, it is believed that the apple peel has greater bioactive potential compared to the apple flesh. The types of phenolics found in the flesh and the peel of the apple differ. For example, the flesh contains catechins, procyanidins, phloridzin, phloretin glycosides, caffeic acid, and chlorogenic acid whereas the peel contains these phenolic compounds in addition to flavonoids, such as quercetin glycosides, that are not found in the flesh (Burda et al., 1990; Escarpa and Gonzalez, 1998; Golding et al., 2001; van der Sluis et al., 2001). Epicatechin is found in apple peels at a concentration that is almost twice as high as the apple flesh (Golding et al., 2001). Apple peels are often discarded during the processing of apple products such as during applesauce production. From a total of 216 million pounds of apples that were processed for canning and applesauce in New York State in the year 2000 (National Agricultural Statistics Service, 2010), Wolfe and colleagues have estimated that approximately 16 million pounds of apple peels were generated as a waste product (Wolfe et al., 2003). However, considering the high antioxidant and bioactive contents of apple peels, it has been postulated that this is a valuable component of the apple and could be utilized as a functional food or value-added ingredient in food products.

2.4 – Production Method

2.4.1 – Method of Manufacture

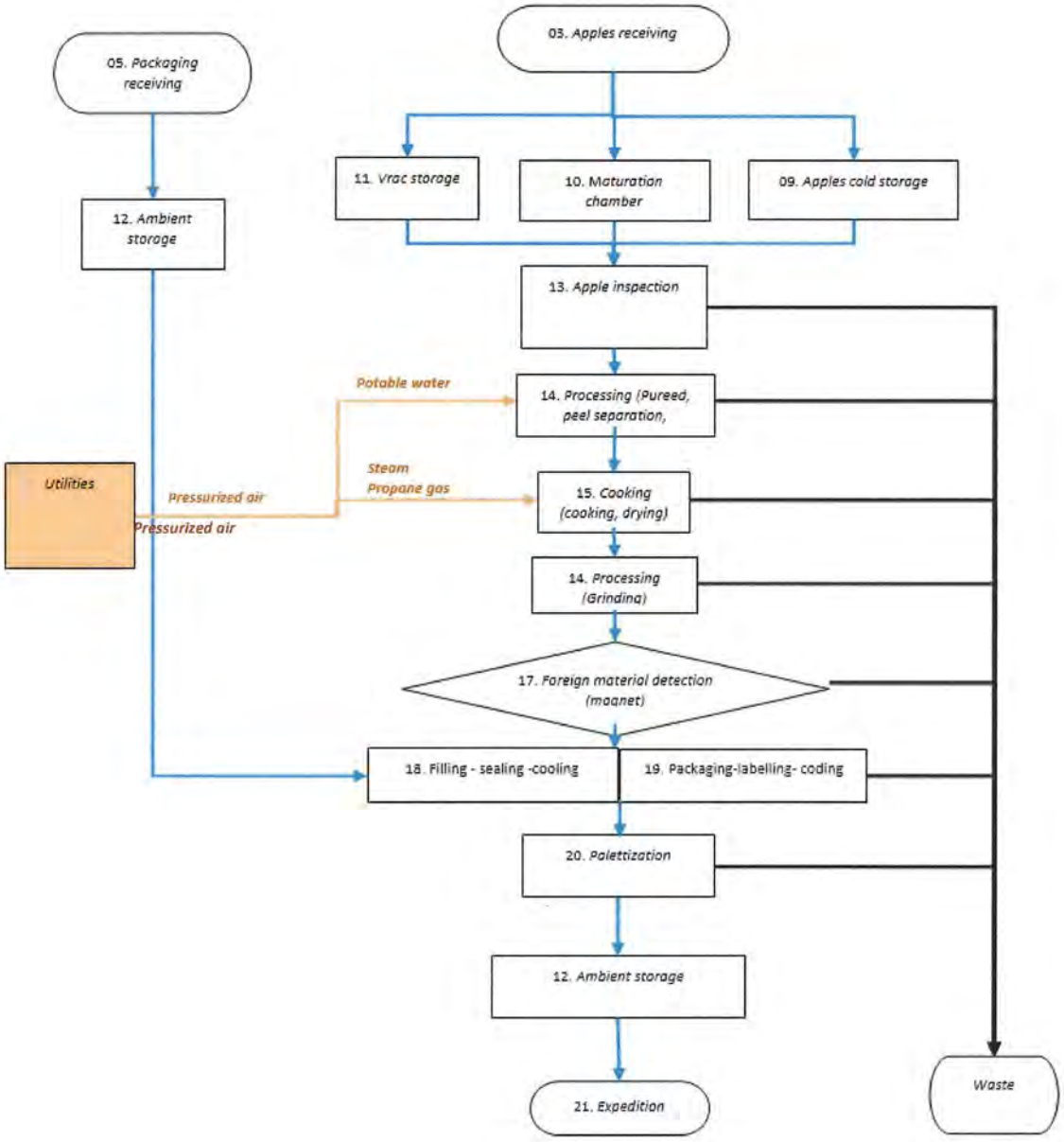
The manufacturing process of AppleActiv™/Leahy DAPP™ is illustrated in the flow diagram (seen below in *Figure 1*) and a description of the manufacturing process, to accompany the flow diagram, follows below:

Preliminary Steps:
- Apple peel origins from a peeling step in apple puree processing.
- Apple peel is separated from the pulp thru sieves.

- Fresh peels from the puree processing are transferred to the Dried Apple Peel Powder processing line.
- The peels from the totes are then transferred to a reception tank.
- From the reception tank, the peels are then "cooked" or pre-heated using hot air.
- From there, the peels are then further dried using dehydrated hot air.
- The peels are then passed through a series of magnets in order to remove any metal contamination.

- The peels are then milled through specific milling equipment.
- The powder is then passed through a second series of magnets in order to remove any metal contamination that may have not been removed the first time the powder was passed through the magnets.
- The dried apple peel powder is then sifted.
- Once the powder has been sifted it is either packaged in drums for bulk storage and labelled, packaged in bottles or in pails, or encapsulated in vegetable capsules.
- Bottles are then packaged in boxes and labelled.
- Boxes are then stored and shipped.

Figure 1 – Flow diagram of the manufacturing process of AppleActiv DAPP™/Leahy DAPP™



2.4.2 – Ingredient Specification and Analytical Methods

The AppleActiv™/Leahy DAPP™ organic apple peel raw material specifications developed by Leahy Orchards is presented below in *Table 2*. These specifications include standards for each of the components of the material, and for the material as a whole which include critical safety attributes specific to DAPP. Included in these specifications are a list of tests, the acceptance criteria for each test, and the analytical methods used to support the acceptance criteria.

***Table 2 – Raw Material Specifications of* AppleActiv™/Leahy DAPP™ (Dried Apple Peel Powder) Proposed by Leahy Orchards Inc.**

Parameter	Analytical Method	Acceptance Criteria
Description		
Appearance	Organoleptic	Light to dark beige fine powder – may include reddish tint
Assay		
Polyphenols/Total Antioxidant Activity	Folin-Ciocalteau GAE	≥ 3.0%
Chemical and Physical Tests		
Loss on Drying	USP <731>	< 7.5%
Particle Size Distribution	USP <786>	≥ 95% through #100 Mesh
Impurities (Heavy Metals)		
Arsenic	U.S. EPA – ICP/MS	≤ 2.0 ppm
Cadmium	U.S. EPA – ICP/MS	≤ 1.0 ppm
Lead	U.S. EPA – ICP/MS	≤ 2.0 ppm
Mercury	U.S. EPA – ICP/MS	≤ 4.0 ppm
Impurities (Pesticides)		
Pesticides	USP <561>	< USP MRL's
Patulin	HPLC/MS	< 50 ppb
Impurities (Microbiology)		
Contaminating Fungi (Yeast and Mold)	USP <2021>	$< 1 \times 10^4$ CFU/g
Total Viable Aerobic Count	USP <2021>	$< 1 \times 10^4$ CFU/g
Salmonella spp.	USP <2022>	Absent
Escherichia coli	USP <2022>	Absent
Staphylococcus aureus	USP <2022>	Absent

Abbreviations: USP - U.S. Pharmacopeia; UV - ultraviolet, cfu – colony forming units, ppm - parts per million. Refer to Appendix 2 – APPLEACTIV DAPP™/LEAHY DAPP™ Organic Apple Peel Raw Material Specification for full report.

In order to demonstrate the reproducibility of the AppleActiv™/Leahy DAPP™ manufacturing process with respect to quality, the analytical results for three batches of raw material (Lot# 7069P-92L, Lot# 7087P-92L and Lot# 7111P-92L) are presented below in *Tables 3A, 3B* and *3C*.

The three batches (Lot# 7069P-92L, Lot# 7087P-92L and Lot# 7111P-92L) were tested for total antioxidant activity (total polyphenols) and impurities (heavy metals, pesticides, and microbiological). Compliance with specifications for total antioxidant activity and impurities, as defined in the Raw Material Specifications (*Table 2*) were demonstrated and the results are presented below in *Tables 3A, 3B* and *3C.*

2.4.2.1 – Analytical Results: Compliance with Specifications

Table 3A **– Analytical Results of AppleActiv™/Leahy DAPP™ Raw Material (Lot# 7069P-92L) to Demonstrate Compliance with Specifications**

Parameter	Analytical Method	Acceptance Criteria	Results
Description			
Appearance	Organoleptic	Light to dark beige fine powder – may include reddish tint	Complies
Assay			
Polyphenols/Total Antioxidant Activity	Folin-Ciocalteau GAE	≥ 3.0%	4.25 %
Chemical and Physical Tests			
Loss on Drying	USP <731>	< 7.5%	2.8%
Particle Size Distribution	USP <786>	≥ 95% through #100 Mesh	97%
Impurities (Heavy Metals)			
Arsenic	U.S. EPA – ICP/MS	≤ 2.0 ppm	< 0.03 ppm
Cadmium	U.S. EPA – ICP/MS	≤ 1.0 ppm	< 0.02 ppm
Lead	U.S. EPA – ICP/MS	≤ 2.0 ppm	0.02 ppm
Mercury	U.S. EPA – ICP/MS	≤ 4.0 ppm	< 0.02 ppm
Impurities (Pesticides)			
Pesticides	USP <561>	< USP MRL's	Complies
Patulin	HPLC/MS	< 50 ppb	Not detected
Impurities (Microbiology)			
Contaminating Fungi (Yeast and Mold)	USP <2021>	< 1 x 10^4 CFU/g	< 10 CFU/g
Total Viable Aerobic Count	USP <2021>	< 1 x 10^4 CFU/g	30 CFU/g
Salmonella spp.	USP <2022>	Absent	Negative
Escherichia coli	USP <2022>	Absent	Negative
Staphylococcus aureus	USP <2022>	Absent	Negative

* Refer to Appendix 2.1 – Specifications and Certificate of Analysis Lot# 7069P-92L for full certificate.

***Table 3B* – Analytical Results of AppleActiv™/Leahy DAPP™ Raw Material (Lot# 7087P-92L) to Demonstrate Compliance with Specifications**

Parameter	Analytical Method	Acceptance Criteria	Results
Description			
Appearance	Organoleptic	Light to dark beige fine powder – may include reddish tint	Complies
Assay			
Polyphenols/Total Antioxidant Activity	Folin-Ciocalteau GAE	≥ 3.0%	4.23 %
Chemical and Physical Tests			
Loss on Drying	USP <731>	< 7.5%	3.6%
Particle Size Distribution	USP <786>	≥ 95% through #100 Mesh	98%
Impurities (Heavy Metals)			
Arsenic	U.S. EPA – ICP/MS	≤ 2.0 ppm	< 0.03 ppm
Cadmium	U.S. EPA – ICP/MS	≤ 1.0 ppm	< 0.02 ppm
Lead	U.S. EPA – ICP/MS	≤ 2.0 ppm	0.48 ppm
Mercury	U.S. EPA – ICP/MS	≤ 4.0 ppm	< 0.02 ppm
Impurities (Pesticides)			
Pesticides	USP <561>	< USP MRL's	Complies
Patulin	HPLC/MS	< 50 ppb	Not detected
Impurities (Microbiology)			
Contaminating Fungi (Yeast and Mold)	USP <2021>	< 1 x 10^4 CFU/g	< 10 CFU/g
Total Viable Aerobic Count	USP <2021>	< 1 x 10^4 CFU/g	< 10 CFU/g
Salmonella spp.	USP <2022>	Absent	Negative
Escherichia coli	USP <2022>	Absent	Negative
Staphylococcus aureus	USP <2022>	Absent	Negative

* Refer to Appendix 2.2 – Specifications and Certificate of Analysis Lot# 7087P-92L for full certificate.

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***Table 3C* – Analytical Results of AppleActiv™/Leahy DAPP™ Raw Material (Lot# 7111P-92L) to Demonstrate Compliance with Specifications**

Parameter	Analytical Method	Acceptance Criteria	Results
Description			
Appearance	Organoleptic	Light to dark beige fine powder – may include reddish tint	Complies
Assay			
Polyphenols/Total Antioxidant Activity	Folin-Ciocalteau GAE	≥ 3.0%	4.36 %
Chemical and Physical Tests			
Loss on Drying	USP <731>	< 7.5%	4.7 %
Particle Size Distribution	USP <786>	≥ 95% through #100 Mesh	97%
Impurities (Heavy Metals)			
Arsenic	U.S. EPA – ICP/MS	≤ 2.0 ppm	< 0.03 ppm
Cadmium	U.S. EPA – ICP/MS	≤ 1.0 ppm	< 0.02 ppm
Lead	U.S. EPA – ICP/MS	≤ 2.0 ppm	0.17 ppm
Mercury	U.S. EPA – ICP/MS	≤ 4.0 ppm	< 0.02 ppm
Impurities (Pesticides)			
Pesticides	USP <561>	< USP MRL's	Complies
Patulin	HPLC/MS	< 50 ppb	Not detected
Impurities (Microbiology)			
Contaminating Fungi (Yeast and Mold)	USP <2021>	< 1 x 10^4 CFU/g	< 10 CFU/g (Yeast) 300 CFU/g (Mold)
Total Viable Aerobic Count	USP <2021>	< 1 x 10^4 CFU/g	< 10 CFU/g
Salmonella spp.	USP <2022>	Absent	Negative
Escherichia coli	USP <2022>	Absent	Negative
Staphylococcus aureus	USP <2022>	Absent	Negative

* Refer to appendix 2.3 Specifications and Certificate of Analysis Lot# 7111P-92L for full certificate.

Part 3 – Dietary Exposure

Intended applications of use for organic dried apple peel powder (DAPP) from *Malus domestica* as a food ingredient include but are not limited to the following:

- Beverages, including fruit and/or vegetable juice products;
- Fortified foods and beverages;
- Milk and milk products;
- Bakery products;
- Dairy products and substitutes;
- Ready-to-eat cereals, sauces, dips, gravies and condiments.

These food categories were identified in the United States Department of Agriculture's (USDA) *Continuing Survey of Food Intakes by Individuals* (1994 – 1996 CFSII) or 21 C.F.R. 101.12, *Reference Amounts Customarily Consumed per Eating Occasion*. The estimated daily intake values for AppleActiv™/Leahy DAPP™ were based on regular consumption patterns of these food categories. The proposed food uses and the percent use level of AppleActiv™/Leahy DAPP™ are summarized below in *Table 1*:

***Table 1* – Summary of the Individual Proposed Uses and Use Levels of AppleActiv™/Leahy DAPP™ in the United States.**

Food Category	Proposed Food Uses	Use Level (%)
Fruits and fruit juices	Applesauce and cooked apples, fruit puree, fruit-based meal replacement drinks	0.8 – 1.6
Vegetables juices	Vegetable-based meal replacement drink	0.4 – 0.8
Milk and Milk Products	Yogurt	0.4 – 0.9
	Ice cream and milk	1.2 – 3.0
Bakery Products	Nutritional bars (e.g. breakfast, granola, meal-replacement, chocolate bars, gluten-free, superfood)	2.5 – 5.0
	Cake (all kinds of cakes and cupcakes, except coffeecakes and cheesecakes)	0.9 – 1.8
	Cookies (all varieties of cookies including sweet crackers such as graham cracker, except brownies)	10.0 – 20.0
	Pies (cobblers, fruit crisps, turnovers, other pastries)	0.8 – 1.6
	Pancakes and waffles	2.5 – 5.0
	Quickbreads and muffins (e.g. cornbread, fruit breads, pumpkin breads, zucchini breads, non-yeast coffee cakes and all kinds of muffins)	1.8 – 3.6
Dairy Products and	Milk, milk-based drinks (e.g. instant	0.3 – 0.7

Substitutes	breakfast, meal replacement, cocoa)	
Ready-to-Eat Cereal	Cereals, granola clusters	2.0 – 3.9
Sauces, Dips, Gravies and Condiments	Major condiments (e.g. catsup, steak sauce, soy sauce, vinegar, teriyaki sauce, marinades)	0.1

Apples are considered one of the most valuable fruit crops in the U.S. as reflected by the amount of apples produced in 2012; an estimated 8.07 billion pounds which was valued at almost $3.1 billion (Agricultural Marketing Resource Center, 2013; National Agricultural Statistics Service, 2012). Apples are grown in every state in the United States and in 29 of those states, apples are grown commercially. Washington State products 70 percent of apples grown in the U.S. and other leading states include New York, Pennsylvania, California and Virginia (Agricultural Marketing Resource Center, 2013). Almost 100 different varieties of apples are grown commercially in the U.S. Of the almost 100 different varieties of apples that are grown, the most popular varieties, account for 90 percent of production in 2006 include: Red Delicious, Gala, Golden Delicious, Granny Smith, Fuji, McIntosh, Rome, Empire, York, Jonathan, Idared, Cortland, Stayman, Newtown and Northern Spy. Two of the leading producers of apple products are Mott's (the leading producer of branded applesauce and apple juice in the U.S.) and TreeTop (the leading producer of apple juice and products).

Of all fruit consumption in the U.S., apples rank as the second-most consumed fruit and are considered to be a significant part of the diet. The average per person consumption rate in the U.S. of all forms of apples in 2012 was 44 pounds. The increased consumption of apples and apple products can be attributed to a number of factors including the availability of new varieties, rising incomes, production expansion in the U.S., a growing and diversified population, the availability of products that better meet the needs of consumer lifestyles and increased awareness of the health benefits (Agricultural Marketing Resource Centre, 2013). Apples are also commonly eaten in various parts of the world, proving to be a significant source of flavonoids in the diet. For example, a Dutch Food Consumption Survey (Hertog et al., 1993) revealed that apples are the third largest contributors of flavonoids (followed by tea and onions) and a study in Finland (Knekt et al., 1997) demonstrated that apples are the top contributors of flavonoids. In the U.S., 22 percent of fruit polyphenols consumed in the American diet come from apples, the largest source of polyphenols (Vinson et al., 2001). The worldwide leader in apple production is China, with a record of 38 million tons harvested in 2010 followed by the U.S., European Union, Turkey and Chile (USDA, 2013). Globally, it has been estimated that 67.5 million metric tons of apples were produced in 2012 (Agricultural Marketing Resource Center, 2013).

Aside from the worldwide dietary consumption of apples, Leahy Orchards Inc. has provided dried apple peel powder (DAPP) under the trademark of AppleBoost™ to two dietary supplement manufacturers in Canada since 2010: Greens+® and Genuine Health. These natural health product manufacturers include Leahy's proprietary AppleBoost™ dried apple peel powder in superfoods and snack bars. A summary of the products is presented in Table 5 and the dose of AppleBoost™ per serving, where applicable. Details regarding these products can

be found on the company websites at http://www.greensplus.com/ and http://www.genuinehealth.com/.

***Table 4* – Summary of Health Supplement Products Containing AppleBoost for Sale in Canada**

Company	Product	Dose of AppleBoost™ per serving
Greens+®	Advanced Multi Raw	350 mg per 8.9 g serving
	Advanced Multi Raw (Vanilla Chai flavor)	350 mg per 8.9 g serving
	Organic Superfood Raw	270 mg per 8.0 g serving
	Flavored Energy Bars Natural or Flavored (chocolate, wild berry)	Listed as ingredient (amount unknown)
	Chia Energy Bar Natural or Chocolate Flavored	Listed as ingredient (amount unknown)
	Organic Energy Bars Natural or Amazon Chocolate Flavored	Listed as ingredient (amount unknown)
	Protein Bar Natural or Flavored (Chocolate and Peanut Butter, Wild Berry, Whey Krisp)	Listed as ingredient (amount unknown)
	Original Superfood Crisp	Listed as ingredient (amount unknown)
Genuine Health	Greens+ O	1200 mg/7.6 g serving
	Greens+ Whole Body Nutrition	1200 mg/32.4 g serving
	Greens+ ActivFuel	300 mg/20.9 g serving
	Greens+ ActivFuel Vegan	300 mg/22.4 g serving

An estimate of the intake of dried apple peel powder based on the proposed food uses and use-levels was calculated using the findings of the 1994-1996 Continue Survey of Food Intake by Individuals (CFSII) and/or the Code of Federal Regulations [CFR] 21 CFR 101.12, Reference Amounts Customarily Consumed per Eating Occasion (Table 5). Consumption of these types of foods by the total U.S. population resulted in an estimated mean all-person intake of AppleActiv™/Leahy DAPP™. Furthermore, the 90th percentile all-person consumption of added AppleActiv™/Leahy DAPP™ from all proposed food uses by the total population was also calculated.

***Table 5* – Summary of the Estimated Daily Intake of AppleActiv™/Leahy DAPP™ from Proposed Foods in the U.S. (1994 – 1996 CSFII Data)**

Food Category[a]	USDA Category[b]	Use Level AppleActiv DAPP™/Leahy DAPP™ grams per serving	Serving Size (grams)	USDA Mean Grams of Food Consumed (All Individuals)	Mean Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)	Mean x 2 Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)	Reference Page No.[‡]
Fruits and fruit juices	Applesauce and cooked apples, fruit puree, fruit-based meal replacement drink	1-2	128	4	0.03-0.06	0.06-0.13	Appendix B, pg. 239
Vegetable juices	Vegetable-based meal replacement drink	1-2	242	45[c]	0.19-0.37	0.38-0.74	Appendix B, pg. 238
Dietary supplements and fortified foods and beverages	Vegetable/superfood powder, protein powder formulas, supplements, protein shakes, smoothies	4.5 – 12	The maximum amount recommended, as appropriate, on the label for consumption per eating occasion, or, in the absence of recommendations, 1 unit, e.g., tablet, capsule, packet, teaspoon(s), etc.	N/A	N/A	N/A	N/A
Milk and milk products	Yogurt	1-2	225	271[d]	1.20-2.41	2.41-4.82	Appendix B, pg. 240
	Ice cream and ice milk	1-2	66	15	0.23-0.45	0.45-0.91	Appendix B, pg. 240
			86		0.17-0.35	0.35-0.70	
Bakery products	Nutritional bars (e.g. breakfast, granola, meal replacement, chocolate bars, gluten-free, superfood)	1-2	40	10[e]	0.25-0.50	0.50-1.00	Appendix B, pg. 236
	Cake (all kinds of cakes and cupcakes, except coffeecake and cheesecake)	1-2	109	9	0.08-0.17	0.17-0.33	Appendix B, pg. 236

	Cookies (all varieties of cookies including sweet crackers such as graham crackers, except brownies)	1-2	10	8	0.80-1.60	1.60-3.20	Appendix B, pg. 236
	Pies (cobblers, fruit crisps, turnovers, other pastries)	1-2	125	7	0.06-0.11	0.11-0.22	Appendix B, pg. 236

Table 5 - continued

Food Category[a]	USDA Category[b]	Use Level AppleActiv DAPP™/Leahy DAPP™ grams per serving	Serving Size (grams)	USDA Mean Grams of Food Consumed (All Individuals)	Mean Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)	Mean x 2 Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)	Reference Page No.[‡]
Bakery Products (cont'd)	Pancakes and waffles	1-2	40[f]	5	0.13-0.25	0.25-0.50	Appendix B, pg. 236
	Quickbreads and muffins (e.g. cornbread, fruit breads, pumpkin breads, zucchini breads, non-yeast coffee cakes, and all kinds of muffins)	1-2	55[g]	6	0.11-0.22	0.22-0.44	Appendix B, pg. 236
Dairy products and substitutes	Milk, milk-based drinks (e.g. instant breakfast, meal replacement, cocoa)	1-2	295	182[h]	0.62-1.23	1.23-2.47	Appendix B, pg. 240
Ready-to-eat cereal	Cereals, granola clusters	1-2	51[i]	16	0.31-0.63	0.63-1.25	Appendix B, pg. 236
Sauces, Dips, Gravies and Condiments	Major condiments (e.g., catsup, steak sauce, soy sauce, vinegar, teriyaki sauce, marinades)	1-2	17	3[i]	0.003	0.005	Appendix B, pg. 243

a Dried apple peel powder (DAPP) to be added to these foods or similar substitutes to the extent not precluded by a food standard
b USDA Food Categories and/or serving sizes were defined as per one of two sources: (1) results of the Foods Commonly Eaten in the United States, Quantities Consumed per Eating Occasion and in a Day, 1994-1996 based on the 24-hour recall dietary intake assessment "Continuing Survey of Food Intakes by Individuals" (CFSII) or (2) the Code of Federal Regulations [CFR] 21 CFR 101.12, Reference Amounts Customarily Consumed per Eating Occasion
c Vegetable juices is categorized under the "Total Tomatoes" Category
d Yogurt is categorized under the "Total Milk" Category

e Oatmeal (under the "Grain-Based Products" Category) utilized as the closest match for nutritional bars
f 40 g represents an average of common serving sizes for pancakes and waffles listed in CSFII 1994-1996
g 55 g represents an average of common serving sizes for quickbreads and muffins listed in CSFII 1994-1996
h Milk and milk-based drinks are categorized under the "Fluid Milk" Category
i 51 g represents an average of common serving sizes for various ready-to-eat cereals listed in CSFII 1994-1996
j Catsup (under the "Condiments Gravies and Fats" Category) utilized as the closest match for sauces, dips gravies and condiments

‡Foods Commonly Eaten in the United States, Quantities Consumed Per Eating Occasion and in a Day, 1994-96, Helen Smiciklas-Wright, Diane C. Mitchell, Sharon J. Mickle, Annetta J. Cook, Joseph D. Goldman. http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/Portion.pdf. *Note: USDA Mean Grams of Food Consumed for "All individuals age 2 and over" were found in Table B (Appendix B) of this reference which represents the mean quantities of foods consumed per person per day for all individuals (i.e. consumers and non-consumers), over both days. These means reflect both the amount and frequency of consumption and represent the population's usual daily intake of the tabulated foods during the 3-year period, 1994-1996.*

As previously mentioned, apple peels contain many healthful compounds that are found in higher concentrations in the apple peels compared to the flesh, including polyphenols and flavonoids such as phloretin glycosides, phloridzin, quercetin and chlorogenic acid. Therefore, the apple peels are rich in antioxidants. Furthermore, AppleActiv DAPP™/Leahy DAPP™ contains more than 50% fiber. A compositional analysis of dried apple peel powder, manufactured by Leahy Orchards Inc. was performed and the nutritional composition of DAPP is outlined below in Table 6.

***Table 6* – Nutritional Composition of AppleActiv DAPP™/Leahy DAPP™**

Nutrient Name	% Daily Value per Serving (100 g)	Value per Serving (100 g)
Protein (g)	10%	5
Total Fat (g)	4%	2.3
Saturated Fat (g)	2%	0.43
Trans Fat (g)	-	0.029
Cholesterol (mg)	1%	3
Sodium (mg)	0%	5
Total Carbohydrate (g)	29%	87
Total Dietary Fiber (g)	208%	52
Sugars (g)	-	20
Energy (kcal)	-	390
Minerals		
Calcium	15%	-
Iron	14%	-
Vitamins		
Vitamin A	15%	-
Vitamin C (mg)	380%	-

Part 4 – Self-Limiting Use Levels

The use of native dried apple peel powder (AppleActiv™/Leahy DAPP™) as a food ingredient is limited by the level that can technically be added to a given beverage or food without jeopardizing its quality and consumer acceptability. The organic acid content in *Malus domestica* apples may have implications for sensory properties of AppleActiv™/Leahy DAPP™. Malic acid is the predominant organic acid found in apples and is highly correlated with titratable acidity as demonstrated in an analysis of fifteen *Malus domestica* cultivars (Nour et al., 2010). Sourness depends on titratable acidity (Lugaz et al., 2005), thereby making this an important chemical characteristic for self-limiting use.

Part 5 – Experience Based on Common Use in Food

The statutory basis for the GRAS conclusion for organic dried apple peel powder (AppleActiv™/Leahy DAPP™) is not based on common use in food.

Part 6 – Narrative

6.1. History of Safe Ingestion of Apple Skins

Apples originated in the Middle East more than 4,000 years ago. There is a long history of humans consuming apples and products made from these fruits. For centuries, apples have been used for their juices and are generally eaten fresh, with their skin intact. Apple skins (peels) are also used as garnishes, in cooked dishes or as an ingredient in a variety of dishes. The fruits are eaten fresh, dried, baked, made into apple butter and apple sauce, candied, in pie and cakes, as juice and cider, fermented into *applejack*, *cidre*, *calvados*, etc. Apple butter and apple sauce are excellent fat substitutes in cakes and muffins. *Appenzeller*, a popular cheese of Switzerland, develops one of its distinctive flavors by being immersed in cider. The flowers can be dipped in batter, deep fried and served sprinkled with sugar, or added to fritter batter. They also yield a light amber honey with a fine aroma and an excellent delicate flavor. A tisane made from apple peels is a very popular in Turkey (Facciola, 1998). Apple peels can be dried, powdered and stored for future usage.

Malus domestica (apples) belongs to the *Rosaceae* family which also includes other edible plants such as apricots, cherries and strawberries; they have been consumed since ancient times and are currently one of the most commonly consumed fruits globally (Shoji et al., 2004). The use of apples in the human diet has been described over thousands of years. Sir Isaac Newton was inspired by apples to formulate his theory of gravitation when he saw an apple fall from a tree. Apples are generally considered healthy when consumed, with the adage, "an apple a day, keeps the doctor away" being often recited when referring to apples. Apples were first introduced to North American by Colonists in the 17th Century; the first apple orchard on the continent of North America was planted in Boston by William Blaxton in 1625 (James, 1980). Apple cultivars brought to North America as seeds from Europe were spread along Native American trade routes, as well as being cultivated on colonial farms. In 1845, the United States apple nursery catalogue sold 350 of the "best" cultivars, showing the proliferation of new North American cultivars by the early 19th Century (James, 1980).

In 2014, global apple production reached 84.6 million tons, with China producing 48% of this total (FAO, 2014). Other major producers with 6% or less of the world total were the United States, Turkey, Poland and Italy (FAO, 2014). Apples constitute one of the most extensively produced and consumed fruits worldwide. In Chile, apple is considered one of the countries major fruits with approximately 1.3 million tons being commercially produced. As previously mentioned, apples are eaten in a number of different ways. The whole fruit, skin included, is suitable for human consumption. The only part of the apple fruit which may not be suitable for human consumption is the seed, which may affect some consumers. However, since the GRAS substance is made of only apple peels, any safety concerns that may arise as a result of the apple seed do not apply. The apple core is often not eaten and is generally discarded. As has been already demonstrated by Facciola (1998) apples are used in a number of different food

products and are consumed in many different ways. Powdered dried apple peel ingredients that have been developed may be used in the formulation of functional foods. They contain nutrients and a series of bioactive phytochemicals that provide a number of benefits to one's health.

There is a growing interest in fruit extracts and dried fruit powders in novel food applications as nutraceutical ingredients or as sources of antioxidants. Various agri-food waste and by-products have been screened for the recovery of natural phenolic antioxidants (Massini et al., 2013). Some nutraceutical products have been developed from apple peels and marketed for the functional markets in the U.S. The apple peels are preferably processed into a dried and pulverized material for nutraceutical use. To the best of our knowledge, the preparation and characterization of apple peel powders for food stabilization has not been studied yet. Moreover, no safety concerns were identified with the intended use of apple peel powder at 5 grams daily in a range of products (smoothies, bars, powdered food products) (AppleActiv DAPP™).

Throughout history, several cookbooks could be found demonstrating the use of apples in many different types of recipes. To date, apples are the most consumed fruit in America and worldwide. According to Economic Research Services (ERS) of the United States Department of Agriculture (USDA), in the year 2014, per capita apple consumption in the United States was 11.6 pounds per person. Americans consumed an average of 119.9 pounds of fresh and processed fruit per person in 2014. Apples (11.6 pounds per person) and bananas (11.3 pounds per person) top the list of most popular consumed fresh fruits (ERS, 2017).

An interest in apples has also grown due to the amount of research being conducted into the potential health benefits of the fruit flesh and fruit juices. Apples are readily available for consumption year-round. Apples provide a balanced intake of various vitamins and minerals, however, the nutrient content of the apple can vary between the different cultivars.

Apples (*Malus domestica*) are the second most commonly consumed fruit in the United States, with 65% of the apple crop consumed as fresh fruit and 35% as processed apple products (e.g. juice, cider, applesauce). Apples with the skin (peel) contain a mix of insoluble (3.1 g per one medium apple) and insoluble (1.3 g per one medium apple) fiber (Nicklas et al., 2015). Apples should be consumed with their peels because discarding the peels reduces the fiber content by up to 25% (Nicklas et al., 2015). Therefore, fiber rich fruit sources, including whole apples with peels should be encouraged among children and adults (Nicklas et al., 2015). One hundred percent fruit juice makes up approximately 35 to 50% of the total fruit intake of children aged 9 to 18 years (Nicklas et al., 2015).

Conceição de Oliveira (2003), investigated the effect of consumption of fruit on body weight change. Hypercholesterolemic, non-smoking, overweight women, 30 to 50 years of age, were randomized to receive, one of three treatments of: apples, pears, or oat cookies. The women were instructed to eat one of each supplement three times a day as snacks between meals. The overall intake of supplements per day was 300 grams of whole apple (providing approximately 35.5 grams of fresh fiber or when dried (see above paragraph), is approximately 8.54 g [using an estimate of ~11.5 % of fiber from apple (21 g of fiber for 182 g of a medium apple] from the

USDA Nutrient Database), 300 grams of pear, or 60 grams of oat cookies. After 12 weeks, the fruit group lost 1.22 kg body weight compared to oat cookies group. A significantly greater decrease of blood glucose was observed among those who had eaten fruits compared with those who had eaten oat cookies. No adverse events were reported in either apple, pear or oat cookie groups. As such, the amount of apple peel (~ 8.54 grams per day of dried apple peel) consumed by the participants in this study exceeds the amount of apple peel powder consumed in one serving of AppleActiv DAPP™/Leahy DAPP™, supporting the safety of the GRAS substance when used in accordance with its intended uses.

The rationale provided above demonstrates the historical significance of apples in the human diet. Apples are commonly consumed and provide a number of health benefits including a natural source of a number of beneficial nutrients and dietary fiber. The above rationale also provides evidence demonstrating how apple peels themselves are consumed both on whole apples and how apple peels are consumed as dishes themselves in different cultures around the world. It is also important to note that the substance for which this GRAS notification has been prepared is composed solely of apple peels that have been dried and powdered (regarded as minimal processing). As such, the substance for which this GRAS notification has been prepared can be considered to be safe for human consumption when used in accordance with its intended uses.

6.2. – Nutritional Composition of Dried Apple Peel Powder

AppleActiv DAPP™/Leahy DAPP™ (Dried Apple Peel Powder) will be used in various foods and beverages (as mentioned in Table 1) at levels not to exceed 5 g per day. As per the USDA Nutrient Database (Table 6 below), the fresh peel from one medium apple weighs approximately 21 grams and when dried to 3% moisture (as in DAPP), will produce 5.04 grams of dried apple peel powder. Therefore, processing one medium apple with skin, will produce 5.04 grams of DAPP. Historically, the safety of consuming one medium apple (with its skin intact) daily is supported as discussed above (Section 6.1).

Apple peels are composed of approximately 50.7% dietary fiber by weight (Chromadex Assay, 2008), of which approximately half is soluble, and half is insoluble (Gorinstein et al., 2001). Apple peel is known to contain 1.2 to 3.3 times more polyphenols than the flesh of the fruit (Roupas & Noakes, 2010). Wolfe and Liu (2003) reported that apple peels have high concentrations of phenolic compounds. Wolfe and Liu (2003) prepared an apple peel powder ingredient on the basis that a valuable food ingredient could be made using the peels of apples if they could be dried and ground to a powder without large losses of phytochemicals. The investigators prepared the dried apple peel powder ingredient and then characterized the phenolic compounds present. The investigators were able to determine that the total phenolic content was 3342 ± 12 mg gallic acid equivalents/100 g dried peels, the flavonoid content was 2299 ± 52 mg catechin equivalents/100 g dried peels, and the anthocyanin content was 169.7 ± 1.6 mg cyanidin 3-glucoside equivalents/100 g dried peels. These phytochemical contents were a significantly higher than those of the fresh apple peels if calculated on a fresh weight basis. Table 6 (below) provides additional information regarding the (basic) nutrient composition of

medium raw apples with and without skin. Furthermore, Table 7 (below) provides the complete nutrition profile of dried apple peel powder Lot# 7069P-92L.

Table 6 – USDA Nutrient Database: Nutrient File (Nutrient Composition of Apple With and Without Skin)

Apple, raw, with skin (09003): one medium fruit (3" dia) = 182 g	**Apple, raw, without skin (09004): one medium fruit (3" dia) = 161 g ***
Water = 155.72 g	Water = 139.54 g
Carbohydrate = 25.13 g	Carbohydrate = 20.54 g
Total fat = 0.31 g	Total fat = 0.21 g
Protein = 0.47 g	Protein = 0.43 g
Total dietary fiber = 4.4 g	Total dietary fiber = 2.1 g
Moisture = 155.7 g	Moisture = 139.54 g
Energy = 95 kcal	Energy = 77 kcal

** Weight of raw apple without skin is reported based on after removal of skin of the weight. Therefore, fresh weight of apple peel is approximately 21 g (per medium apple). (dia = diameter)*

Furthermore, the Reference Amount Customarily Consumed per eating occasion for apples (as per 21 CFR 101.12) is 140 g. According to the USDA Nutrient Database (Basic Report: 09003 Apples, raw, with skin & Basic Report: 09004 Apples, raw, without skin) one medium sized raw apple with skin is 182 g and one medium sized raw apple without skin is 161 g. Based on these two values, it can be estimated that the apple peel is approximately 21 g per medium apple. When comparing the amount of water in an apple with its skin intact (155.72 g) to an apple that has had its skin removed (139.54 g), it can be assumed that 16.18 g of water is lost when the apple is peeled. Based on this amount, it can be assumed that 16.18 g of the total mass of the apple peel (21 g per medium apple) is water. Furthermore, the remaining 4.82 grams of total mass in the peel consists of various nutrients such as carbohydrates, fiber and various minerals and nutrients. The amount of dried apple peel powder provided by AppleActiv DAPP™/Leahy DAPP™ based on its intended uses would be a maximum of 5 grams per person per day in a range of products. As demonstrated by the USDA Nutrient database basic reports for raw apples with and without their skins, it can be seen that the apple peel consists mainly of water and other nutrients. As the amount of apple peel provided by a daily serving of AppleActiv DAPP™/Leahy DAPP™ is lower than the 90th percentile of dietary apple consumption and the composition of apple peel being 77% water with the remaining composition consisting of commonly consumed nutrients, it can be concluded that the recommended proposed levels of AppleActiv DAPP™/Leahy DAPP™ are safe for human consumption.

As such, the substance for which this GRAS notification has been prepared can be considered to be safe for human consumption when used in accordance with its intended uses.

***Table 7* – Nutrition Profile of Dried Apple Peel Powder (DAPP) from Lot# 7069P-92L**

DAPP BIO; Lot# 7069P-92L (61362-1)

Test	Specification	Test Result	Method	Analyst	Date
Fructose	N/A	10.4%	HPLC-RI	HR	2017-05-23
Sucrose	N/A	4.24%	HPLC-RI	HR	2017-05-23
Galactose/Glucose	N/A	3.90%	HPLC-RI	HR	2017-05-23
Maltose	N/A	0.00%	HPLC-RI	HR	2017-05-23
Lactose	N/A	0.00%	HPLC-RI	HR	2017-05-23
Sugars	N/A	18.5%	HPLC-RI	HR	2017-05-23
Vitamin D	N/A	0.00 mg	HPLC-UV	AP	2017-05-23
Iron	N/A	4.26 mg	ICP-MS	GK	2017-05-25
Sodium	N/A	242 mg	ICP-MS	GK	2017-05-25
Calcium	N/A	643 mg	ICP-MS	GK	2017-05-25
Potassium	N/A	822 mg	ICP-MS	GK	2017-05-25
Moisture	N/A	1.46%	Oven-Drying at 105 C	SA	2017-05-25
Ash	N/A	3.17%	AOAC 923.03	SA	2017-05-25
Protein	N/A	7.31%	AOAC TKN	DB	2017-05-23
Trans-Fatty Acids	N/A	0.00 mg	AOAC 996.06	IL	2017-05-25
Fat, Total	N/A	5.65%	AOAC Solvent Extraction	DB	2017-05-23
Saturated Fatty Acids	N/A	583 mg	AOAC 996.06	IL	2017-05-25
Cholesterol	N/A	0.00 mg	AOAC 994.10	IL	2017-05-25
Dietary Fibre, Total	N/A	56.3%	AOAC 992.16/985.29	AQ	2017-05-23
Carbohydrates, Total	N/A	82.4%	Calculation	YYU	2017-05-26
Calories, Total	N/A	410 kcal	Calculation	YYU	2017-05-26

*Based on a unit weight of 100000 mg.

Abbreviations: AOAC, Association of Official Agricultural Chemists; HPLC, high-performance liquid chromatography; (Refer to Appendix 4 – APPLEACTIV DAPP™/LEAHY DAPP™ full report of nutrition composition)

6.3. – Research Studies

This section addresses the safety of Dried Apple Peel Powder through a comprehensive review of scientific literature which forms the basis of the self-determination of GRAS status. In the subsequent sections, preclinical studies (*in vitro* and *in vivo*) and human studies investigating various apple products (including polyphenols which are a constituent of apple peels) will be reviewed to assess the toxicological profile of AppleActiv DAPP™/Leahy DAPP™. Collectively, all information has been reviewed to establish an empirical base for GRAS status of Dried Apple Peel Powder, in concert with providing a strong basis for safety.

Overall, it can be seen that apple peels contain naturally occurring polyphenolic compounds. These polyphenolic compounds exist naturally in a number of fruits and vegetables that are also commonly consumed on a daily basis. Furthermore, the substance for which this GRAS

notification has been prepared is made solely of apple peels that have been dried and powdered. As such, this substance poses no safety related issues when used in accordance with its intended uses. The substance for which this GRAS notification has been prepared can be considered to be safe for human consumption when used in accordance with its intended uses.

6.3.1. – Safety of Consumer Exposure to Apple Peel Polyphenols

Polyphenol components have a long history of safe consumption by humans as they commonly occur in various fruits and vegetables. Apples are a very popular fruit worldwide and in the U.S., they alone are estimated to account for 20-25% of the per capita fruit polyphenol consumption (Ceymann et al., 2017). As polyphenols are the most abundant antioxidants in apple peels, consumption of whole apples (with peels) contributes to an overall intake of antioxidants. Polyphenols in general contain one or more aromatic rings and at least two hydroxyl groups. There are five main polyphenol classes found in apples, namely flavan-3-ols, phenolic acids, dihydrochalcones, flavonols and anthocyanidins (Ceymann et al., 2013). Although apple peel contains high levels of polyphenols, the absorption rate for the individual polyphenols are estimated to be low. In addition, rapid metabolism of the polyphenols complicates the investigation of polyphenol absorption (Ceymann et al., 2017).

The average 100 grams fresh weight of fruits (e.g. grapes, apple, pear, cherries and berries) contains up to 300 mg of polyphenols (Ganesan & Xu., 2017). Typically, a cup of tea or coffee or a glass of red wine contains more than 100 mg of polyphenols (Ganesan & Xu., 2017). Due to the frequent consumption of apples and their varying polyphenol content and profile, modulating polyphenols in apples or apple by-products may be a possible nutritional tool to support the prevention of chronic health conditions. To provide the relevant data for estimating the potential for adverse health effects of apples, the following section deals with the history of safe polyphenol consumption.

The content of phenolic compounds, dietary fiber and minerals are higher in the apple peel compared to other edible parts of the fruit (Henriguez et al., 2010). Furthermore, Henriguez et al (2010) developed a novel ingredient of dried apple peel from Granny Smith apple peel and demonstrated that dried apple peel could be considered a good source of phenolic compounds (38.6 mg gallic acid equivalent/g dry basis) and dietary fiber (39.7% dry basis) in the formulation of value added foods. Moreover, in terms of processing of apple peels, drum drying is a simple and energy efficient procedure that retains over 30% of the phenolic compounds in the apple peel (Henriguez et al., 2010).

Generally polyphenolic compounds are widely distributed throughout the plant kingdom. As such, they are present in most edible fruits and vegetables and are therefore common in the daily diet of most individuals. Although relevant progress has been made in defining the distribution and content of other flavonoids in foods, including monomeric catechins (e.g. catechin and epicatechin), the information available on anthocyanidins (one of the major polyphenol compounds found in apple peels) is somewhat limited. Large variations exist in the

reported concentrations for any given product or commodity. Moreover, Scalbert et al (2000) cited the intake of polyphenols (from all sources) to be approximately 1 g/day with phenolic acids accounting for one third and flavonoids accounting for the remaining two thirds (Scalbert et al, 2000). However, it is difficult to estimate the exact intake of polyphenols due to lack of comprehensive data on polyphenol compounds in foods.

The amount of measured Polyphenols (as assayed by the Folin-Ciocalteau method of Gallic acid equivalence, GAE) of AppleActiv DAPP™/Leahy DAPP™ is ~ 4.23 – 4.36% which equates to ~ 212 - 218 mg of gallic acid equivalence as an approximation of polyphenol content per 5 grams serving of AppleActiv DAPP™/Leahy DAPP™. This level of polyphenol content is well below the stated amount of cited phenolic acids intake per day of 1 grams (Scalbert et al., 2000). Overall, the safety of polyphenols, including those from apples, is well recognized as described above.

6.3.2. – Toxicology Studies of Apple Polyphenol Extract

A summary of the results of the toxicology studies referenced (obtained through a literature search or those conducted by the applicant) are presented below in Table 8. A more detailed description of each study consulted follows subsequently. Furthermore, human clinical trials demonstrating the safety of apple peel polyphenol extracts can also be found in section 6.3.2.3. Based on the rationale provided below, it can be seen that the polyphenolic content of apples (peel intact) is well tolerated as demonstrated by the clinical evidence seen *in vitro* and *in vivo* in both animals and humans. All of the studies consulted in the preparation of this rationale demonstrated that the polyphenolic content of apple peels is well tolerated over a range of doses and that no adverse events reported in the studies are attributable to the consumption of polyphenols from apple peels. As such, the substance for which this GRAS notification is being prepared can be considered to be safe for human consumption when consumed in accordance with its intended use. Furthermore, as a major constituent, polyphenols do not have toxicological concerns as assessed in various *in vitro* and *in vivo* studies.

Table 8 **– Summary Table of the Pre-Clinical Toxicological Studies Conducted Using Apple Polyphenol Extract**

Study Type	Study Reference	Source	Results	Section
In vitro reverse mutation test (AMES test) and chromosomal	Shoji et al., 2004	Applephenon® Apple Polyphenol Extract	No significant mutagenicity	6.3.2.1.

aberration test				
In vitro reverse mutation test (AMES test) and mouse lymphoma assay	Lina et al., 2012	Evesse™ EPC Apple Polyphenol Extract	Positive mutagenicity	6.3.2.1
In vivo 14-day acute oral toxicity and 90-day oral subchronic toxicity tests	Shoji et al., 2004	Applephenon® Apple Polyphenol Extract (obtained from unripe whole apples)	Lethal dose of Applephenon® >2000 mg/kg did not produce any clinical signs, adverse effects or deaths in the animals tested	6.3.2.2.
In vivo 90-day oral subchronic toxicity study	Lina et al., 2012	Evesse™ EPC Apple Polyphenol Extract	NOAEL of 2% Evesse™ EPC in the diet (1.3 and 1.5 g/kg bw/day for male and female rats respectively)	6.3.2.2.
In vivo	Jia et al., 2017	Apple Peel Polyphenolic Extract (obtained from unripe whole apples)	The daily dose of 600 and 900 mg apple peel polyphenolic extract in this study did not produced any toxic or adverse effects	6.3.2.2.
In vivo	Denis et al., 2016	Dried Apple Peel Powder	The investigators did not report any toxic or adverse effects while administering 200 and 400 mg/kg/day of dried apple peel powder	6.3.2.2.

6.3.2.1. *In Vitro* Genotoxicity Studies

Shoji et al (2004) demonstrated that a polyphenol extract obtained from unripe whole apples (Applephenon®, Asahi Breweries Ltd., Japan) resulted in a slight increase in the number of revertants in *Salmonella thyphimurium* strain T198 in a reverse mutation test (AMES Test) using cultured mammalian cells at a dose of 2,500 mg/plate. However, there was no increase in revertants at a dose of 5,000 mg/plate in any of the other bacterial strains of *Salmonella thyphimurium* tested, including TA, 100 TA1535 and TA1537 or of *Escherichia coli* (WP2 uvrA). An *in vitro* chromosomal aberration test using Chinese Hamster Lung (CHL) cells did not reveal any abnormalities with Applephenon® at a dose of 0.313 mg/mL. Therefore, the *in vitro* tests conducted demonstrate that Applephenon® did not result in any significant mutagenicity.

The bacterial reverse mutation test (AMES Test) in accordance with OECD testing guideline No. 471 was also conducted using another polyphenol extract rich in flavan-3-ols (Evesse™ EPC) at test concentrations ranging from 62 mcg to 5,000 mcg/plate in triplicate cultures (Lina et al., 2012). Five strains of the bacterium *Salmonella typhimurium* (TA 1535, TA 1537, TA 98, TA 100) and one of the tryptophan-requiring strain of *Escherichia coli* (WP2 uvrA) in the presence or absence of a metabolic activation system (S9 mix) were used. Evesse™ EPC showed slight toxicity in two strains of *S. typhimurium* (TA 1537 and TA 98) in the absence and presence of S9 as demonstrated by a greater than two-fold increase in the mean number of revertants compared to the concurrent negative control but not in a clearly dose-related manner. No other bacterial strains showed signs of toxicity or mutagenicity.

In the second *in vitro* experiment conducted by Lina et al. (2012), the mouse lymphoma assay (conducted according to OECD testing guideline No. 476), L5178Y thymus tissue cells were treated in duplicate at concentrations of Evesse™ EPC ranging from 7 to 3,000 mcg/ml (4 hours) with S9 and 8 to 1,000 mcg/ml (24 hours) without S9. Evesse™ EPC demonstrated a toxic response to the cells in a dose-dependent manner; in the absence of S9 at doses of 610 mcg/ml and greater and in the presence of S9 at the dose of 2,600 mcg/ml, an induced mutant frequency of > 126 mutants/1,000,000 clonable cells was observed. Therefore, in the absence of S9, a biologically relevant increase in mutant frequency was observed (at least 10% reduction of initial cell yield) whereas in the presence of S9, the increase in cells, combined with less than a 10% reduction of initial cell yield, was not considered indicative for mutagenicity.

Altogether, these results demonstrate that Evesse™ EPC was considered mutagenic *in vitro* due to the results of both the bacterial reverse mutation test and the mouse lymphoma assay at acceptable levels of cytotoxicity. The authors commented on the alignment of the results observed in the present study with those obtained in previous *in vitro* and *in vivo* genotoxicity studies investigating other polyphenols. The formation of reactive oxygen species *in vitro* provides a possible explanation of the positive mutagenicity observed with Evesse™ EPC. It is also important to note the general consensus of the high prevalence of false positive results obtained through *in vitro* genotoxicity assays using mammalian cells, such as the mouse lymphoma assay used in the present study. In section 6.3.2.2., which pertains to *in vivo* studies, the absence of genotoxic effects in an animal study also conducted by Lina et al. (2012) will be discussed.

The above noted studies provides evidence that there is no safety concerns in terms of mutagenicity or genotoxicity for extracts of apples with high levels of polyphenols; thus, providing further safety support for the substance for which this GRAS notification is being prepared.

6.3.2.2. – *In Vivo* Toxicity Studies

In a study conducted by Shoji et al. (2004), Applephenon® (an apple polyphenol extract powder) was administered to male (n=5) and female (n=5) 5-week old Sprague-Dawley (Crj:CD) rats at a dose of 2,000 mg/kg. The powder was dissolved in a 0.5% CMC-Na (sodium carboxymethyl cellulose) solution; 10 ml/kg of the sample was then injected intragastrically by direct stomach intubation. General condition and body weight were monitored for 14 days after administration. On day 14, all animals were sacrificed and subjected to necropsies. The following organs were examined: heart, spleen, trachea, lungs, stomach, duodenum, ileum, jejunum, cecum, colon, rectum, liver, kidneys, urinary bladder, testis, pituitary, thyroids, parathyroid, adrenal gland, brain, submaxilliary glands, thymus, seminal vesicle, prostate, ovary and uterus. The investigators concluded that no significant changes were observed in any organs at the necropsy on day 14. The investigators determined that the acute oral minimum fatal dose of Applephenon® for Sprague-Dawley rats is > 2,000 mg/kg body weight.

Subsequently, a 90-day subchronic oral toxicity test also conducted in Sprague-Dawley rats was also conducted by Shoji et al. (2004). Applephenon® was administered to groups of 6-week old male (n=10) and female (n=10) Sprague-Dawley rats at the concentrations of 0, 500, 1,000, and 2,000 mg/kg by intragastric injection of 10 ml/kg of the sample using direct stomach intubation. The general physical condition of each animal was observed throughout the 90-day test period and food consumption was measured once a week. On day 90, a blood sample was collected from the abdominal aorta of each animal. The blood sample was analyzed for a number of different hematological parameters. The investigators demonstrated that doses as high as 1,000 mg/kg of body weight in females and 2,000 mg/kg body weight in males did not result in any changes in clinical signs, adverse effects or deaths in any of the animals tested. The only differences between the test and control groups with respect to changes in body weight was attributed to normal biological variation, and not the administration of Applephenon® (Shoji et al., 2004).

Taken altogether, these two *in vivo* studies demonstrate that at a dose as high as 2000 mg/kg body-weight no significant hematological, clinical, chemical, histopathological or urinary effects compared to the controls were reported. Furthermore, the dose of 2000 mg/kg body-weight utilized in the 90-day subchronic study is equivalent to the human consumption of 272 apples/day per 60 kg body weight, which represents a 120-fold higher dose than the estimated average human dietary intake of apples. Therefore, the average total dietary intake of polyphenols in humans is estimated to be much less than the levels that were shown to be safe in these *in vivo* studies.

Lina et al. (2012) conducted a 90-day subchronic toxicity test in male and female Wistar rats in accordance with OECD guideline No. 408. In four groups of ten rats each, doses of 0% (controls), 1.25%, 2% and 3.25% (w/w) Evesse™EPC was added to diet for 13 consecutive weeks. Body weight was monitored over the course of the study and hematology, clinical chemistry, quantitative urinalysis, and organ weight data were evaluated. Dietary levels up to 3.25% Evesse™EPC was well tolerated, showing no effects on health, neurobehavioural endpoints or results of opthalmospcopy. Other effects noted considered attributable to treatment (i.e. changes in body weight) were not dose-related or clinically significant (i.e. changes in hematological, clinical chemistry and urinalysis parameters). Other observed effects were likely due to biological variation and were not considered as adverse (i.e. changes in organ weights). Overall, Evesse™EPC administration did not result in changes of toxicological significance. A NOAEL was determined at a dietary concentration of 2% Evesse™EPC. This is equivalent to an overall average intake of 1.3 g/kg bw/day in male rats and 1.5 g/kg bw/day in female rats. The authors reported a dose of 13 mg/kg bw/day Evesse™EPC as an acceptable intake in humans utilizing a 100-fold safety margin. This is equivalent to approximately 910 mg Evesse™EPC that provides approximately 275 mg epicatechin daily for a 70 kg adult.

Jia et al. (2017), investigated the preventive effects of red fuji apple polyphenolic extracts (APP) on vascular endothelial dysfunction and liver injury in mice fed a high choline diet. Results of this study demonstrated that mice fed with APP at 600 and 900 mg/ kg body-weight (equivalent to 2.9 g and 4.4 g per 60kg BW human respectively) significantly increased serum NO, HDL and 6-Keto-PGF1a levels and lowered serum TC, TG, LDL, ET-1 and TXB2 levels compared to mice fed with 3% dietary choline for 8 weeks. The daily dose of 600 and 900 mg apple polyphenols in this study did not produced any toxic or adverse effects thus supporting safety of this constituent of dried apple peel powder, which is richer in polyphenols compared to the apple pulp as noted previously.

Denis et al., (2016), evaluated the therapeutic aspects of polyphenols in dried apple peel powder (DAPP) on intestinal inflammation while elucidating the underlying mechanisms and clinical benefits in mice. Induction of intestinal inflammation in the mice was performed by oral administration of the inflammatory agent dextran sulfate sodium (DSS) at 2.5% for 10 days. Physiological and supraphysiological doses of DAPP (200 and 400 mg/kg/day respectively) were administered by gavage for 10 days pre- and post-DSS treatment. Results of this study demonstrated that DAPP is safe for consumption. Furthermore, the investigators make note that the concentrations of phenolic extract administered to their mice model approximates the total extractable phenolic content of 100 g of fresh apple that is widely consumable by humans (~ 357 mg/100 g fresh apple). In addition, the investigators also make note that the phenolic doses used in their study in mice are easily attainable in humans by applying the U.S. FDA's guidelines to establish the human equivalent dose based on body surface area. Moreover, DAPP exhibits powerful antioxidant and anti-inflammatory action in the intestine of mice and evaluation of preventive and therapeutic effects of DAPP may be clinically feasible in individuals with intestinal inflammatory bowel conditions at an equal dose of 0.975g and 1.95g per day for an average 60 kg body weight adults.

6.3.2.3. – Human Clinical Studies

There is a body of clinical evidence that supports the safe use of dried apple peel-derived polyphenols for various functional applications. These studies are described in detail below.

The safety of an excessive intake and the efficacy of a long-term intake of apple-derived polyphenols was examined in a randomized, double-blind, placebo-controlled study (Akazome et al. 2010). Subjects consumed a beverage with or without 600 mg of apple polyphenols. To assess long-term safety, subjects were administered 340 g of the beverage each day for 12 weeks; to assess excessive intake, subjects were administered the beverage thrice daily for 4 weeks. This study confirmed the safety of its test beverage (apple derived polyphenols) as no clinical problems arose in either the long-term intake or excessive intake trials (Azakome et al. 2010).

Kishi et al (2005) investigated the effects of a 500 mg/day dose of apple polyphenols on the treatment of cedar pollinosis in a 12-week, double-blind comparative study. With respect to safety, no changes were apparent throughout the study relating to the subjective symptoms of the subjects, nor to hematological or serum biochemical tests (Kishi et al., 2005).

A randomized double-blind, placebo-controlled study administered 600 mg/day of capsules containing polyphenols extracted from apples and hop bract to moderately obese male and female subjects (71 subjects) with a body mass index ranging from 23 to 30 (Nagasako-Akazome et al., 2007). This study demonstrated the safety of the treatment dose, as no adverse reactions were observed during the study. Moreover, no adverse events reported were reported during the completion of this study therefore supporting the safety of daily doses of 600 mg of apple polyphenols.

Recently, Jensen et al (2014) evaluated the effects of consumption of dried apple peel powder (DAPP) on joint function and range of motion (ROM). This was an open-label clinical pilot study that involved 12 healthy human subjects with moderate loss of joint ROM and associated chronic pain. The subjects consumed 4.25 g DAPP (a product from Leahy Orchards) daily for 12 weeks, with evaluations at baseline, 2, 4, 8 and 12 weeks respectively. Participants consumed three capsules three times daily, for a daily dose of 4.25 g, which is the upper daily dose recommended by the manufacturer. Results of this study demonstrate that consumption of DAPP for 12 weeks was associated with a statistically significant improvement in serum antioxidant protective status. Furthermore, the daily dose of 4.25 g DAPP in this study was well tolerated supporting the safety of DAPP. Overall, there is a growing appreciation and understanding of the link between fruit and vegetable consumption and improved health (Hyson, 2011). Apples have been included in health-related studies around the world due to their rich content of varied phytochemicals and fiber.

6.3.3. – Allergenicity

As presented in the Allergen Declaration (Appendix 4), Leahy Orchards Inc. has demonstrated that AppleActiv DAPP™/Leahy DAPP™ does not contain the following common allergens and has come into minimal contact during manufacturing:

- Peanuts
- Tree nuts (including coconut and its derivatives)
- Sesame seeds
- Dairy products
- Eggs
- Fish
- Shellfish
- Crustaceans
- Soy products
- Mustard
- Wheat
- Gluten (barley, oats, rye triticale, wheat, all species including kamut and spelt)
- Sulphites

Aside from making a declaration of the presence of these above components in AppleActiv DAPP™/Leahy DAPP™ to notify individuals with food allergies, sensitivities or intolerances, an attempt was made to determine the prevalence of hypersensitivity to raw fruits, including apples, through a literature search. In individuals allergic to birch pollen, there is an increased likelihood of an allergic reaction to apples. The relationship between hypersensitivity to raw fruits and vegetables and respiratory allergy to birch pollen has been well established. In a recent European study which investigated the prevalence and distribution of food sensitization in adults, food IgE sensitization to apples was 6.5% which was highly correlated with the prevalence of pollen-associated allergens (Burney et al., 2014). A study of this nature conducted in the U.S. was not found, but these findings suggest that there is subset of the population which may present with a hypersensitivity to apple and that this food allergy is likely to be cross-react with an allergy to birch pollen.

6.4. – Summary and Basis for GRAS

Conclusion

The standard for GRAS has become "reasonable certainty of no harm under the intended conditions of use." The FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following elements:

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and

- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of expert panels or opinions from authoritative bodies, such as the National Academy of Sciences.

The first common knowledge element for a GRAS determination is that data and information relied upon to establish safety must be generally available; this is most commonly established by utilizing published, peer-reviewed scientific journals for the safety assessment. The second common knowledge element required for a GRAS determination is that consensus among qualified scientists about the safety of the substance with its intended use must be demonstrated. Results from the toxicity studies demonstrate lack of overt toxicity of the commercial product as manufactured and demonstrate the lack of mutagenic impurities.

Based on the above data and information presented herein, Leahy has concluded that the intended food uses of AppleActiv DAPP™/Leahy DAPP™ as described in Table 5, are GRAS based on scientific procedures. General recognition of Leahy's GRAS determination is supported by the unanimous consensus of individuals with experience and scientific training, to evaluate the use of AppleActiv DAPP™/Leahy DAPP™ in food, who similarly concluded that the intended uses of AppleActiv DAPP™/Leahy DAPP™ as described herein are GRAS. Food uses of AppleActiv DAPP™/Leahy DAPP™ as described herein may therefore be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21, Section 170.3 of the Code of Federal Regulations.

Part 7 – List of Supporting Data and Information

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APPENDIX

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Appendix 2.1 – Specifications and Certificate of Analysis (Lot# 7069P-92L)

AppleActiv DAPP™

Organic Apple Peel Powder - Certificate of Analysis

Product Name:	AppleActiv DAPP™ - Dried Apple Peel Powder		
Botanical (Latin):	*Malusdomestica*	**Part used:**	Fruit Peel
CAS #:	89957-68-2	**Country of Origin:**	Canada
Lot #:	7069P-92L	**Manufacturing Date:**	March 10, 2017
Shelf Life:	4 years when properly stored.		
Storage:	Preserve in tight, light-resistant containers, in a cool, dry place.		
Product Description:	Light to dark beige fine powder - may include reddish tint		
Certification	USDA Organic GMP licensed facility		

Parameter		Reference Method	Specification	Results
Description				
Appearance		Organoleptic	Light to dark beige fine powder - may include reddish tint	Complies
Assay47				
Polyphenols/Total Antioxidant Activity		Folin-Ciocalteau GAE	≥ 3,00 %	4,25 %
Specific Tests (Chemical & Physical)				
Loss on Drying		USP <731>	< 7,5 %	2,8%
Particle Size Distribution		USP <786>	≥ 95% through #100 mesh	97%
Impurities				
Heavy Metals	As	USEPA-ICP/MS	< 2,0 ppm	<0,03 ppm
	Cd	USEPA-ICP/MS	< 1,0 ppm	<0,02 ppm
	Hg	USEPA-ICP/MS	< 4,0 ppm	<0,02 ppm
	Pb	USEPA-ICP/MS	< 2,0 ppm	0,02 ppm
Pesticides		USP <561>	< USP MRL's	Complies
Patulin		HPLC/MS	< 50 ppb	Not detected
Microbiology				
Contaminating Fungi (Yeast & Molds)		USP <2021>	< 1 X 10^4cfu/g	< 10 cfu/g
Total viable aerobic count		USP <2021>	< 1 X 10^4cfu/g	30 cfu/g
Salmonella spp.		USP <2022>	Absent	Negative
Escherichia coli		USP <2022>	Absent	Negative
Staphylococcus aureus		USP <2022>	Absent	Negative

* Refer to the chemical residue specifications list included herein for MRL's.
* Absent as determined by USP method.
* AppleActiv DAPP has been manufactured within a dedicated manufacturing line and is a Gluten Free product.
* Our heavy metal limits respect the limits establish in Proposition 65

Date issued/Revised: 2017-04-04 Reviewed By: Marie-Pier Lanoue

Signature: (b) (6)

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Appendix 2.2 – Specifications and Certificate of Analysis (Lot# 7087P-92L)

AppleActiv DAPP™

Organic Apple Peel Powder - Certificate of Analysis

Product Name:	AppleActiv DAPP™ - Dried Apple Peel Powder		
Botanical (Latin):	*Malusdomestica*	**Part used:**	Fruit Peel
CAS #:	89957-48-2	**Country of Origin:**	Canada
Lot #:	7087P-92L	**Manufacturing Date:**	March 28, 2017
Shelf Life:	4 years when properly stored.		
Storage:	Preserve in tight, light-resistant containers, in a cool, dry place.		
Product Description:	Light to dark beige fine powder - may include reddish tint		
Certification	USDA Organic GMP Licensed facility		

Parameter		Reference Method	Specification	Results
Description				
Appearance		Organoleptic	Light to dark beige fine powder - may include reddish tint	Complies
Assay47				
Polyphenols/Total Antioxidant Activity		Folin-Ciocalteau GAE	≥ 3,00 %	4,23 %
Specific Tests (Chemical & Physical)				
Loss on Drying		USP <731>	< 7,5 %	3,8%
Particle Size Distribution		USP <786>	≥ 95% through #100 mesh	98%
Impurities				
Heavy Metals	As	USEPA-ICP/MS	< 2,0 ppm	<0,03 ppm
	Cd	USEPA-ICP/MS	< 1,0 ppm	<0,02 ppm
	Hg	USEPA-ICP/MS	< 4,0 ppm	<0,02 ppm
	Pb	USEPA-ICP/MS	< 2,0 ppm	0,48 ppm
Pesticides		USP <561>	< USP MRL's	Complies
Patulin		HPLC/MS	< 50 ppb	Not detected
Microbiology				
Contaminating Fungi (Yeast & Molds)		USP <2021>	< 1 X 10^cfu/g	< 10 cfu/g
Total viable aerobic count		USP <2021>	< 1 X 10^cfu/g	< 10 cfu/g
Salmonella spp.		USP <2022>	Absent	Negative
Escherichia coli		USP <2022>	Absent	Negative
Staphylococcus aureus		USP <2022>	Absent	Negative

* Refer to the chemical residue specifications list included herein for MRL's.
* Absent as determined by USP method.
* AppleActiv DAPP has been manufactured within a dedicated manufacturing line and is a Gluten Free product.
* Our heavy metal limits respect the limits establish in Proposition 65

Date Issued/Revised: 2017-05-01 Reviewed By: Marie-Pier Lazure

Signature: (b) (6)

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Appendix 2.3 – Specifications and Certificate of Analysis (Lot# 7111P-92L)

AppleActiv DAPP™

Organic Apple Peel Powder - Certificate of Analysis

Product Name:	AppleActiv DAPP™ - Dried Apple Peel Powder		
Botanical (Latin):	*Malusdomestica*	**Part used:**	Fruit Peel
CAS #:	89957-48-2	**Country of Origin:**	Canada
Lot #:	7111P-92L	**Manufacturing Date:**	April 21, 2017
Shelf Life:	4 years when properly stored.		
Storage:	Preserve in tight, light-resistant containers, in a cool, dry place.		
Product Description:	Light to dark beige fine powder - may include reddish tint		
Certification	USDA Organic GMP Licensed facility		

Parameter		Reference Method	Specification	Results
Description				
Appearance		Organoleptic	Light to dark beige fine powder – may include reddish tint	Complies
Assay47				
Polyphenols/Total Antioxidant Activity		Folin-Ciocalteau GAE	≥ 3,00 %	4,36 %
Specific Tests (Chemical & Physical)				
Loss on Drying		USP <731>	< 7,5 %	4,7
Particle Size Distribution		USP <786>	≥ 95% through #100 mesh	97%
Impurities				
Heavy Metals	As	USEPA-ICP/MS	< 2,0 ppm	<0,03 ppm
	Cd	USEPA-ICP/MS	< 1,0 ppm	<0,02 ppm
	Hg	USEPA-ICP/MS	< 4,0 ppm	<0,02 ppm
	Pb	USEPA-ICP/MS	< 2,0 ppm	0,17 ppm
Pesticides		USP <561>	< USP MRL's	Complies
Patulin		HPLC/MS	< 50 ppb	Not detected
Microbiology				
Contaminating Fungi (Yeast & Molds)		USP <2021>	< 1 X 10^cfu/g	< 10 cfu/g (yeast) 300 cfu/g (mold)
Total viable aerobic count		USP <2021>	< 1 X 10^cfu/g	< 10 cfu/g
Salmonella spp.		USP <2022>	Absent	Negative
Escherichia coli		USP <2022>	Absent	Negative
Staphylococcus aureus		USP <2022>	Absent	Negative

* Refer to the chemical residue specifications list included herein for MRL's.
* Absent as determined by USP method.
* AppleActiv DAPP has been manufactured within a dedicated manufacturing line and is a Gluten Free product.
* Our heavy metal limits respect the limits establish in Proposition 65

Date Issued/Revised: 2017-07-10 Reviewed By: Marie-Pier Lazure

Signature: (b) (6)

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Appendix 3 – Nutrition Profile of Dried Apple Peel Powder (Lot# 7069P-92L)

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LABS-MART

REPORT # 61362-1

To Les Vergers Leahy Orchards Inc.
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Date 2017-05-26
Received 2017-05-19

DAPP BIO; Lot# 7069P-92L (61362-1)

Test	Specification	Test Result	Method	Analyst	Date
Fructose	N/A	10.4%	HPLC-RI	HR	2017-05-23
Sucrose	N/A	4.24%	HPLC-RI	HR	2017-05-23
Galactose/Glucose	N/A	3.90%	HPLC-RI	HR	2017-05-23
Maltose	N/A	0.00%	HPLC-RI	HR	2017-05-23
Lactose	N/A	0.00%	HPLC-RI	HR	2017-05-23
Sugars	N/A	18.5%	HPLC-RI	HR	2017-05-23
Vitamin D	N/A	0.00 mg	HPLC-UV	AP	2017-05-23
Iron	N/A	4.26 mg	ICP-MS	GK	2017-05-25
Sodium	N/A	242 mg	ICP-MS	GK	2017-05-25
Calcium	N/A	643 mg	ICP-MS	GK	2017-05-25
Potassium	N/A	822 mg	ICP-MS	GK	2017-05-25
Moisture	N/A	1.46%	Oven-Drying at 105 C	SA	2017-05-25
Ash	N/A	3.17%	AOAC 923.03	SA	2017-05-25
Protein	N/A	7.31%	AOAC TKN	DB	2017-05-23
Trans-Fatty Acids	N/A	0.00 mg	AOAC 996.06	IL	2017-05-25
Fat, Total	N/A	5.65%	AOAC Solvent Extraction	DB	2017-05-23
Saturated Fatty Acids	N/A	583 mg	AOAC 996.06	IL	2017-05-25
Cholesterol	N/A	0.00 mg	AOAC 994.10	IL	2017-05-25
Dietary Fibre, Total	N/A	56.3%	AOAC 992.16/985.29	AQ	2017-05-23
Carbohydrates, Total	N/A	82.4%	Calculation	YYU	2017-05-26
Calories, Total	N/A	410 kcal	Calculation	YYU	2017-05-26

*Based on a unit weight of 100000 mg.

Prepared by (b) (6)
Yang Yu, Senior Analyst

Approved by (b) (6)
Feng Jia, QA/QC Manager

Date 2017-05-26

Raw data are archived by Labs-Mart Inc. Results shown relate only to samples submitted and tested.
Labs-Mart Inc. reserves all rights of interpretation of its test results. It assumes no liability for the use of the results by any party.
Testing may be completed at other Labs-Mart locations.

Page 1 of 1

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Appendix 4 – Allergen Declaration

leahy

ALLERGEN DECLARATION

Product name : AppleActiv™ Organic Leahy DAPP™ (Dried apple peel powder)

Plant Location: Franklin Centre ***County :*** Canada

Product	Colonne/*Column* I Present in the product	Colonne/*Column* II Present in other products manufactured on the same line	Colonne/*Column* III Present in the same manufacturing plant
Peanuts	NO	NO	NO
Tree nuts (including coconut and its derivatives)	NO	NO	YES (Coconut)
Sesame Seeds	NO	NO	NO
Dairy Products	NO	NO	NO
Eggs	NO	NO	NO
Fish	NO	NO	NO
Shellfish	NO	NO	NO
Crustaceans	NO	NO	NO
Soy Products	NO	NO	NO
Mustard	NO	NO	NO
Wheat	NO	NO	NO
Gluten (barley, oats, rye, triticale, wheat (all species including kamut and spelt))	NO	NO	YES (Oat flour)
Sulphites (please indicate levels in ppm)	NO	NO	YES (Sodium Metabisulphite)

Is there an efficient program in place to avoid cross-contamination of the products with allergens not present in the product, but declared in columns II and III?

☒ Oui/*Yes* ☐ Non/*No* ☐ n/a

Completed by : (b) (6) **Date :** 2017-07-28

VERGERS LEAHY inc. – LEAHY ORCHARDS Inc.
vergersleahy.com / leahyorchards.com
tel 450 827-2544
fax 450 827-2470

Health Canada / Santé Canada

DESIGNATED PARTY AUTHORIZATION FORM

Natural Health Products Directorate

Protected when completed

FORMULAIRE D'AUTORISATION DE LA PARTIE DÉSIGNÉE

Direction des produits de santé naturels

Protégé une fois rempli

Note: Only submit this document with the application when the party signing the application is a designated party acting on behalf of the applicant or licensee according to paragraph 5(*b*) of the *Natural Health Products Regulations*. A separate authorization is required for each application.

Note : Ne présenter ce document avec la demande que lorsque la partie désignée signe la demande au nom du demandeur ou du titulaire conformément à l'alinéa 5(*b*) du *Règlement sur les produits de santé naturels*. Une autorisation distincte est obligatoire pour chaque demande.

I / Je Lorraine Leahy (The Senior Official / Agent principal) authorize / donne l'autorisation à Monica Banach (Third party person / Tierce partie) of / de Dicentra, Inc (Third party company name / Nom de l'entreprise de la tierce partie) to file a submission with the Natural Health Products Directorate on behalf of / de remplir une présentation à la Direction des produits de santé naturels au nom de **/or to file a submission with the FDA on behalf of:** **Leahy Orchards Inc** (Applicant/Company name / Nom du demandeur/de l'entreprise)

(b) (6)

Lorraine Leahy
Print Name / Nom en lettres moulées

Director Functional Foods
Title / Titre

Leahy Orchards Inc
Applicant/Company name / Nom du demandeur/de l'entreprise

Date: 2018 01 15

CONTACT INFORMATION/RENSEIGNEMENTS SUR LE TITULAIRE

Surname / Nom de famille	Mr. / M.	Ms. / Mme	Dr.	Given Name / Prenom
Banach	☐	☒	☐	Monica

Title / Titre	Language preferred / Langue de preference
Regulatory and Scientific Associate	☒ English / Anglais ☐ French / Français

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603-7 St. Thomas Street

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Toronto	ON	Canada	M5S 2B7

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416 361 3400	231	416 361 3304	monica@dicentra.com

HC/SC 9273 (01-2004)

Canada

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Health Canada / Santé Canada

DESIGNATED PARTY AUTHORIZATION FORM

Natural Health Products Directorate

Protected when completed

FORMULAIRE D'AUTORISATION DE LA PARTIE DÉSIGNÉE

Direction des produits de santé naturels

Protégé une fois rempli

Note: Only submit this document with the application when the party signing the application is a designated party acting on behalf of the applicant or licensee according to paragraph 5(*b*) of the *Natural Health Products Regulations*. A separate authorization is required for each application.

Note : Ne présenter ce document avec la demande que lorsque la partie désignée signe la demande au nom du demandeur ou du titulaire conformément à l'alinéa 5(*b*) du *Règlement sur les produits de santé naturels*. Une autorisation distincte est obligatoire pour chaque demande.

I / Moi, Lorraine Leahy (The Senior Official / Agent principal) authorize all active* contacts of / je donne pouvoir à toutes les personnes-resources actuelles de

Dicentra, Inc (Third party company name / Nom de l'entreprise de la tierce partie) to file a submission with the Natural Health Products Directorate on behalf of / de remplir une présentation à la Direction des produits de santé naturels au nom de /or to file a submission with the FDA on behalf of: Leahy Orchards Inc (Applicant/Company name / Nom du demandeur/de l'entreprise)

(b) (6)

Lorraine Leahy
Print Name / Nom en lettres moulées

Director, Functional Foods
Title / Titre

Leahy Orchards Inc
Applicant/Company name / Nom du demandeur/de l'entreprise

*The third party senior official is responsible for notifying NHPD of any changes to their affiliated contacts.

Date
2018 01 15

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LIFE SCIENCES CONSULTING

October 22, 2018

U.S. Food and Drug Administration
Center for Food Additive Safety
Office of Food Additive Safety
Attn: Molly Harry

RE: GRN 000805 (apple peel powder)

Dear Ms. Harry,

Thank you very much for the comments related to GRN 000805 (apple peel powder) submitted on behalf of Leahy Orchards Inc. To address the questions raised by the review team we have provided our responses below.

We look forward to continued communication and should there be additional clarification please feel reach out to us.

1) *On page 21, the notice provides estimates of dietary exposure to apple peel powder for each of the intended food categories (Table 5). Please provide an overall mean and 90th percentile estimate of exposure from the intended use of apple peel powder in all food categories.*

   As per the provided Table 5 in the GRAS notice, estimates of the consumption of AppleActiv™/Leahy DAPP™ from the various food categories was provided. Based on this information it is expected that the mean intake of the powder will be 4.183 – 8.353 g/day and the approximate 90th percentile will be 8.365-16.715 g/day. This is presented in Table 1 at the end of this document.

2) *On Page 28, the notice states that "Apples with the skin (peel) contain a mix of insoluble (3.1 g per one medium apple) and insoluble (1.3 g per one medium apple) fiber (Nicklas et al. 2015)." The notice provides two values for insoluble fiber, please clarify which one of these amounts relates to the insoluble fiber?*

   As per Nicklas et al. 2015, apples (with skin) contain a mix of insoluble (3.1 g/1 medium apple) and soluble (1.3 g/1 medium apple) fiber.

3) *The notice does not contain a discussion on the absorption, distribution, metabolism and excretion (ADME) of the apple peel powder. Please provide a narrative or discussion of the ADME of apple peel powder.*

AppleActiv™/Leahy DAPP™ is made from 100% dried apple peels that are sourced solely from orchard apples (*Malus domestica*) that are grown in North America (CAS#: 89957-48-2). The peel of the apple contains a much higher concentration of phenolic compounds compared to the flesh and other edible parts of the apple (Wolfe et al., 2003; Podsedek et al., 2000; Liu et al., 2001; Burda et al., 1990; Escarpa and Gonzalez, 1998; Ju et al., 1996). In addition, the phenolics found in in the peel of the apple include catechins, procyanidins, phloridzin, phloretin glycosides, caffeic acid, and chlorogenic and flavonoids, such as quercetin glycosides (Burda et al., 1990; Escarpa and Gonzalez, 1998; Golding et al., 2001; van der Sluis et al., 2001).

In Lee (2012) the pharmacokinetics of Quercetin forms from apple peel powder (AP) with respect to absorption of (C_{max}, t_{max}, and $AUC_{0-24\ h}$) and elimination (k_{el} and $t_{1/2}$) was investigated in healthy volunteers (eight females and eight males). Applesauce with dried apple peel (AP) was provided to volunteers contained ~100 mg of quercetin aglycone equivalents. Consumption of the AP resulted in C_{max} = 63.8 ± 22.4 ng/mL, t_{max} = 2.9 ± 2.0 h, and $t_{1/2}$ = 65.4 ± 80.0 h for total quercetin. No significant gender-related differences were observed in the absorption of quercetin, whereas significant gender-related differences in the elimination half-time ($t_{1/2}$) were observed. (Lee, 2012)

The pharmacokinetic properties of 350 ml of a polyphenol-rich juice drink containing apple dihydrochalcones, procyanidins and chlorogenic acid was investigated in a study often human volunteers after having followed a low-flavonoid diet for 2 days. The juice drink also contained green tea flavan-3-ols, grape seed and pomace procyanidins, and citrus flavonones and grape anthocyanins. Specifically, the dihydrochalcone metabolite, phloretin-20-O-glucuronide, yielded a Cmax of 204± 26 nmol/L, and a short t_{max}, 0.6± 0.1 h with a small secondary peak at 4 hours. This observation was similar to a previous study for apple cider as noted by the study authors. The authors noted that the overall excretion of dihydrochalcone metabolites suggested that absorption mainly occurred in the small intestine, within the first 5 hours of ingestion and with an overall 4.9% of intake corresponding to the observed excretion. For the procyanidins, there were no detectable dimers, trimers or pentamers of procyanidins in the plasma or urine samples. For the chlorogenic acid hesperetin-7-O-rutinoside, the urinary metabolites accounted for 12% of the 45 umol of this ingested compound, with most excretion occurring 2-8 hours after ingestion. Along with the plasma pharmacokinetic profile, this suggests that the absorption of the hesperetin compound occurs in the small and large intestine. Overall, as the plasma pharmacokinetics and recoveries of urinary metabolites of several polyphenols (namely, flavan -3-ols, flavanones, dihydrochalcones and 5-0-caffeoylquinic acid), were similar to other feeding

studies with respect to identity and quantity, it was determined that the polyphenolic compounds in the beverage are absorbed and excreted to a similar extent whether fed individually or together in a single beverage (Borges et al., 2010).

Apple peels are composed of approximately 50.7% dietary fiber by weight of which approximately half is soluble, and half is insoluble (Gorinstein et al., 2001). Pectic substances, common soluble fibers in apple peels, are a complex group of polysaccharides in which D-galacturonic acid is a principal constituent. They are structural components of plant cell walls and act as intercellular cementing substances. Pectin is highly water-soluble and is almost completely metabolized by colonic bacteria when consumed (Dhingra, et al., 2012).

4) *In Section 6.3.1 of the notice (page 32), you discuss the polyphenol components of apple peel powder with a supporting reference by Ceymann. The notice cites the publication date variably as 2013 and 2017 respectively. Please provide an updated page 13 with the correct date for the Ceymann publication.*

The correct in text citation for all the Ceymann references is Ceymann, 2013. Attached is the updated page 13 with this correction made.

Kind Regards,

Monica Banach, MSc Pharmaceutical Sciences
Scientific Regulatory Affairs Specialist

References

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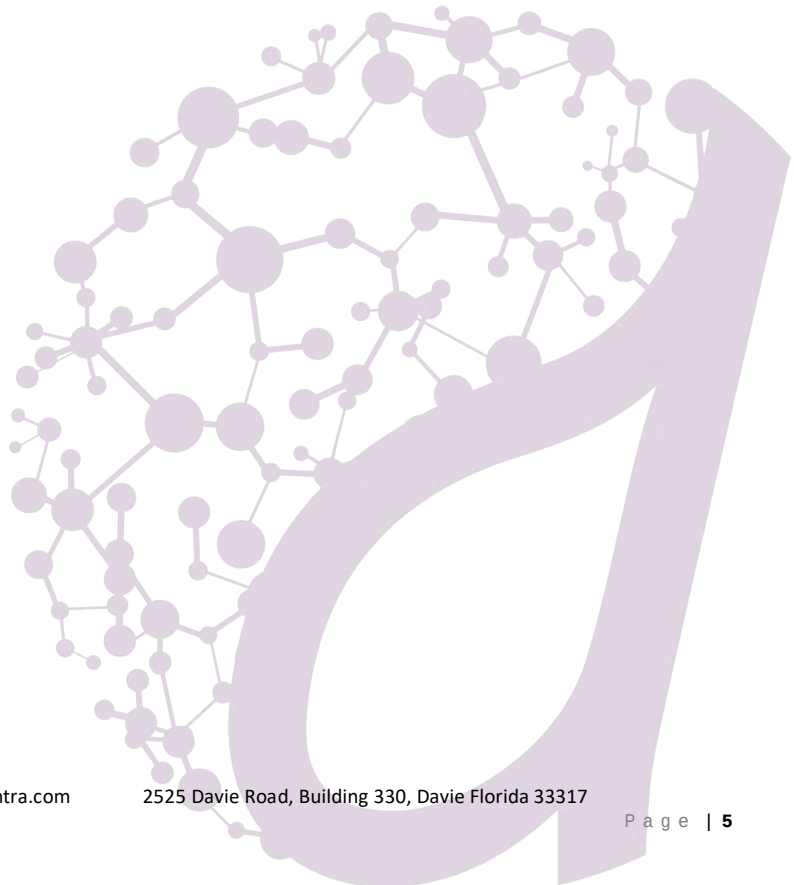

***Table 1* – Summary of the Estimated Daily Intake of AppleActiv™/Leahy DAPP™ from Proposed Foods in the U.S. (1994 – 1996 CSFII Data)**

Food Category[a]	USDA Category[b]	Use Level AppleActiv DAPP™/Leahy DAPP™ grams per serving	Serving Size (grams)	USDA Mean Grams of Food Consumed (All Individuals)	Mean Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)	Mean x 2 Grams AppleActiv DAPP™/Leahy DAPP™ Consumed (All Individuals)
Fruits and fruit juices	Applesauce and cooked apples, fruit puree, fruit-based meal replacement drink	1-2	128	4	0.03-0.06	0.06-0.13
Vegetable juices	Vegetable-based meal replacement drink	1-2	242	45[c]	0.19-0.37	0.38-0.74
Dietary supplements and fortified foods and beverages	Vegetable/superfood powder, protein powder formulas, supplements, protein shakes, smoothies	4.5 – 12	The maximum amount recommended, as appropriate, on the label for consumption per eating occasion, or, in the absence of recommendations, 1 unit, e.g., tablet, capsule, packet, teaspoon(s), etc.	N/A	N/A	N/A
Milk and milk products	Yogurt	1-2	225	27 1[d]	1.20-2.41	2.41-4.82

	Ice cream and ice milk	1-2	66	15	0.23-0.45	0.45-0.91
			86		0.17-0.35	0.35-0.70
Bakery products	Nutritional bars (e.g. breakfast, granola, meal replacement, chocolate bars, gluten-free, superfood)	1-2	40	10[e]	0.25-0.50	0.50-1.00
	Cake (all kinds of cakes and cupcakes, except coffeecake and cheesecake)	1-2	109	9	0.08-0.17	0.17-0.33
	Cookies (all varieties of cookies including sweet crackers such as graham crackers, except brownies)	1-2	10	8	0.80-1.60	1.60-3.20
	Pies (cobblers, fruit crisps, turnovers, other pastries)	1-2	125	7	0.06-0.11	0.11-0.22
Bakery Products (cont'd)	Pancakes and waffles	1-2	40[f]	5	0.13-0.25	0.25-0.50
	Quickbreads and muffins (e.g. cornbread, fruit breads, pumpkin breads, zucchini breads, non-yeast coffee cakes, and all kinds of muffins)	1-2	55[g]	6	0.11-0.22	0.22-0.44
Dairy products and substitutes	Milk, milk-based drinks (e.g. instant breakfast, meal replacement, cocoa)	1-2	295	18 2[h]	0.62-1.23	1.23-2.47
Ready-to-eat cereal	Cereals, granola clusters	1-2	51[i]	16	0.31-0.63	0.63-1.25

Sauces, Dips, Gravies and Condiments	Major condiments (e.g., catsup, steak sauce, soy sauce, vinegar, teriyaki sauce, marinades)	1-2	17	3[j]	0.003	0.005
Mean Total Consumption					**4.183 – 8.353 g**	**8.365-16.715 g**

a Dried apple peel powder (DAPP) to be added to these foods or similar substitutes to the extent not precluded by a food standard
b USDA Food Categories and/or serving sizes were defined as per one of two sources: (1) results of the Foods Commonly Eaten in the United States, Quantities Consumed per Eating Occasion and in a Day, 1994-1996 based on the 24-hour recall dietary intake assessment "Continuing Survey of Food Intakes by Individuals" (CFSII) or (2) the Code of Federal Regulations [CFR] 21 CFR 101.12, Reference Amounts Customarily Consumed per Eating Occasion
c Vegetable juices is categorized under the "Total Tomatoes" Category
d Yogurt is categorized under the "Total Milk" Category
e Oatmeal (under the "Grain-Based Products" Category) utilized as the closest match for nutritional bars
f 40 g represents an average of common serving sizes for pancakes and waffles listed in CSFII 1994-1996
g 55 g represents an average of common serving sizes for quickbreads and muffins listed in CSFII 1994-1996
h Milk and milk-based drinks are categorized under the "Fluid Milk" Category
i 51 g represents an average of common serving sizes for various ready-to-eat cereals listed in CSFII 1994-1996
j Catsup (under the "Condiments Gravies and Fats" Category) utilized as the closest match for sauces, dips gravies and condiments

‡Foods Commonly Eaten in the United States, Quantities Consumed Per Eating Occasion and in a Day, 1994-96, Helen Smiciklas-Wright, Diane C. Mitchell, Sharon J. Mickle, Annetta J. Cook, Joseph D. Goldman. http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/Portion.pdf.
Note: USDA Mean Grams of Food Consumed for "All individuals age 2 and over" were found in Table B (Appendix B) of this reference which represents the mean quantities of foods consumed per person per day for all individuals (i.e. consumers and non-consumers), over both days. These means reflect both the amount and frequency of consumption and represent the population's usual daily intake of the tabulated foods during the 3-year period, 1994-19

Section 6.3.1 of Generally Recognized as Safe (GRAS) Determination for the Use of AppleActiv DAPP™/Leahy DAPP™ (Dried Apple Peel Powder) in Conventional Foods

Submitted By:
Leahy Orchards Inc.
Franklin, Quebec, Canada

Prepared For:
United States Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
5001 Campus Drive
College Park, MD 20740

Prepared By:
Leahy Orchards Inc.
1772 Route 209, Franklin, Quebec, Canada J0S 1E0
and
dicentra LLC
2525 Davie Road, Building 330, Davie, Florida 33317

6.3.1. – Safety of Consumer Exposure to Apple Peel Polyphenols

Polyphenol components have a long history of safe consumption by humans as they commonly occur in various fruits and vegetables. Apples are a very popular fruit worldwide and in the U.S., they alone are estimated to account for 20-25% of the per capita fruit polyphenol consumption (Ceymann, 2013). As polyphenols are the most abundant antioxidants in apple peels, consumption of whole apples (with peels) contributes to an overall intake of antioxidants. Polyphenols in general contain one or more aromatic rings and at least two hydroxyl groups. There are five main polyphenol classes found in apples, namely flavan-3-ols, phenolic acids, dihydrochalcones, flavonols and anthocyanidins (Ceymann, 2013). Although apple peel contains high levels of polyphenols, the absorption rate for the individual polyphenols are estimated to be low. In addition, rapid metabolism of the polyphenols complicates the investigation of polyphenol absorption (Ceymann, 2013).

The average 100 grams fresh weight of fruits (e.g. grapes, apple, pear, cherries and berries) contains up to 300 mg of polyphenols (Ganesan & Xu., 2017). Typically, a cup of tea or coffee or a glass of red wine contains more than 100 mg of polyphenols (Ganesan & Xu., 2017). Due to the frequent consumption of apples and their varying polyphenol content and profile, modulating polyphenols in apples or apple by-products may be a possible nutritional tool to support the prevention of chronic health conditions. To provide the relevant data for estimating the potential for adverse health effects of apples, the following section deals with the history of safe polyphenol consumption.

The content of phenolic compounds, dietary fiber and minerals are higher in the apple peel compared to other edible parts of the fruit (Henriguez et al., 2010). Furthermore, Henriguez et al (2010) developed a novel ingredient of dried apple peel from Granny Smith apple peel and demonstrated that dried apple peel could be considered a good source of phenolic compounds (38.6 mg gallic acid equivalent/g dry basis) and dietary fiber (39.7% dry basis) in the formulation of value added foods. Moreover, in terms of processing of apple peels, drum drying is a simple and energy efficient procedure that retains over 30% of the phenolic compounds in the apple peel (Henriguez et al., 2010).

Generally polyphenolic compounds are widely distributed throughout the plant kingdom. As such, they are present in most edible fruits and vegetables and are therefore common in the daily diet of most individuals. Although relevant progress has been made in defining the distribution and content of other flavonoids in foods, including monomeric catechins (e.g. catechin and epicatechin), the information available on anthocyanidins (one of the major polyphenol compounds found in apple peels) is somewhat limited. Large variations exist in the reported concentrations for any given product or commodity. Moreover, Scalbert et al (2000) cited the intake of polyphenols (from all sources) to be approximately 1 g/day with phenolic acids accounting for one third and flavonoids accounting for the remaining two thirds (Scalbert

et al, 2000). However, it is difficult to estimate the exact intake of polyphenols due to lack of comprehensive data on polyphenol compounds in foods.

The amount of measured Polyphenols (as assayed by the Folin-Ciocalteau method of Gallic acid equivalence, GAE) of AppleActiv DAPP™/Leahy DAPP™ is ~ 4.23 – 4.36% which equates to ~ 212 - 218 mg of gallic acid equivalence as an approximation of polyphenol content per 5 grams serving of AppleActiv DAPP™/Leahy DAPP™. This level of polyphenol content is well below the stated amount of cited phenolic acids intake per day of 1 grams (Scalbert et al., 2000). Overall, the safety of polyphenols, including those from apples, is well recognized as described above.

Section 6.3.1 Specific References

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