RAMBOLL

ENVIRONMENT
& HEALTH

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

RE: GRAS NOTIFICATION FOR RENMATIX NOURAVANT™ MAPLE FIBER

Date September 22, 2020

On behalf of Renmatix Inc., I am pleased to submit this Notification of the Generally Recognized as Safe (GRAS) Determination for Renmatix Nouravant™ Maple Fiber. This Notification contains the expert evaluation report on the GRAS Status of Maple Fiber prepared by Joseph V. Rodricks, PhD, DABT and Duncan Turnbull, DPhil, DABT of Ramboll US Corporation, who are "experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food" according to the criteria of 21 CFR 170.30.

All of the information supporting the safety of Maple Fiber cited in this document is publicly available.

Please contact me (dturnbull@ramboll.com) if you have any questions about this submission.

Yours sincerely

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Prepared for

Renmatix, Inc.

Document type

GRAS Notice

Date

September 2020

Generally Recognized as Safe (GRAS) Assessment of Renmatix Nouravant® Maple Fiber

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Contents

Part 1. Signed Statements and Certification 1

1.1 GRAS Notice Submission 1

1.2 Name and Address of Organization 1

1.3 Substance Name 1

1.4 Intended Conditions of Use 1

1.5 Statutory Basis for Conclusions 1

1.6 Exemption from Premarket Approval 1

1.7 Availability of Data and Information to FDA 2

1.8 Freedom of Information Act (FOIA) 2

1.9 Certifications 2

1.10 Name(s) and Positions(s) of Signatories 2

Part 2. Identity, Method of Manufacture, Specifications, and Physical or Technical Effect 3

2.1 Scientific Data and Information that Identifies the Notified Substance 3

2.1.1 Substance Name, Origin, Composition, and Other Characteristic Properties 3

2.1.2 CAS Registry Numbers 3

2.1.3 Empirical and Structural Formulas 3

2.1.4 Characteristic Properties 5

2.2 Source and Description of Manufacture 5

2.2.1 Hemicellulose Hydrolysis 6

2.2.2 Water Washing 6

2.2.3 Supercritical Hydrolysis 6

2.2.4 Washing and Separation 6

2.2.5 Optional Decolorization Step 6

2.2.6 Finishing Process 7

2.3 Specifications 7

2.4 Batch Analysis Results 8

2.5 Analysis of Potential By-Products 9

2.6 Particle Size 10

2.7 Impurities and Contaminants 11

Part 3. Dietary Exposure 12

3.1 Generation of the Special Split Values 12

3.2 Generation of the Consumption Data 13
Part 4. Self-Limiting Levels of Use 18
Part 5. Experience Based on Common Use in Food Before 1958 19
Part 6. Narrative 20
6.1 Introduction 20
6.2 Safety Assessment Based on Analogy to other Cellulose- and Lignin-containing Plant Fibers 20
6.2.1 Safety Assessment Based on Pecan Shell Fiber (GRN 646) 22
6.3 Safety Assessment of Cellulose 23
6.3.1 Nanocellulose data 24
6.4 Safety Assessment of Lignin 25
6.5 Potentially Toxic Components of Wood 27
6.6 Safety of Potential By-Products 27
6.6.1 Oligomer 28
6.6.2 Glucose 28
6.6.3 Safety of Other Byproducts 28
6.6.3.1 Acetic Acid 29
6.6.3.2 Formic Acid 29
6.6.3.3 Glyceraldehyde 30
6.6.3.4 Glycolic Acid 30
6.6.3.5 Levulinic Acid 31
6.7 Conclusions 31
Part 7. List of Supporting Data and Information 32

Tables and Figures

Tables

Table 1. RENMATIX NOURAVANT® M*aple Fiber* Compositions 3
Table 2. Maple Fiber Release Specifications 8
Table 3. Results of Analysis of Six Recent, Non-consecutive Batches of Nouravant® H1 Maple Fiber 8
Table 4. Results of Analysis of Six Recent, Non-consecutive Batches of Nouravant® H2 Maple Fiber 9
Table 5. Usage Levels of the Renmatix Product by Food Categories 14
Table 6. Consumption Levels by Users in g/kg Body Weight/day 15
Table 7. Composition of Cell-Wall Polymers in Food (g/100g) (Southgate et al. 1986) 20
Table 8. Cellulose and Lignin as Percent of Whole Foods (Southgate et al. 1986) 20
Table 9. Cellulose and Lignin Content of Plant Fiber Products Identified as GRAS 21
Table 10. Lignin Content of Some Foods 26
Table 11. Lignin Content of Foods (as Eaten) 26
Table 12. Estimated Daily Consumption of Maple Fiber Components (mg/kg bw/day) 28

Figures

Figure 1. Cellulose Chemical Structure 3
Figure 2. Example of Lignin Structure 4
Figure 3. Primary Phenols in Lignin 5
Figure 4 Flowchart for Supercritical Hydrolysis of Cellulosic Feedstocks 6
Figure 5. Optional Decolorization Process 7
Figure 6. Finishing Process 7
Figure 7. Average Particle Size Distribution of Nouravant® Maple Fiber (Based on Data from 120 Samples, outliers removed) 11

Part 1. Signed Statements and Certification

1.1 GRAS Notice Submission

In accordance with 21 CFR Part 170, Subpart E, Ramboll US Corporation (Ramboll), on behalf of Renmatix, Inc., submits this Generally Recognized as Safe (GRAS) notice to the U.S. Food and Drug Administration (FDA) for the products of Renmatix's Plantrose® process. This process uses supercritical water to treat plant biomass to separate and isolate sugar monomers and oligomers, cellulose, and lignin. The focus of this document is one of the cellulose + lignin products produced by the process, which is then processed into maple fiber.

The use of maple fiber described herein is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for food additives because it is GRAS through scientific procedures and common use in food prior to 1958, as established in Section 201(s) of the FD&C Act and 21 CFR 170.3. The GRAS evaluation has been conducted by Ramboll US Corporation.

1.2 Name and Address of Organization

Submitted by:

_____ Date: September 22, 2020

Duncan Turnbull, D.Phil., DABT
Senior Managing Consultant
Ramboll US Corporation (Agent)

On behalf of:

Jennifer L. Miller
Chief Legal Officer, Senior Vice President and Secretary
Renmatix, Inc.
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1.3 Substance Name

The subject of this notice is maple fiber manufactured using Renmatix's Plantrose® process.

1.4 Intended Conditions of Use

Renmatix's maple fiber is intended for use as a food ingredient for some of the same range of uses as microcrystalline cellulose or cellulose gel (FCC 2016). It may also replace texturizers such as xanthan or guar gum, and emulsifiers such as lecithin in some applications.

1.5 Statutory Basis for Conclusions

Renmatix's maple fiber is GRAS through scientific procedures in accordance with 21 CFR § 170.30(a) and (b).

1.6 Exemption from Premarket Approval

The substance for this notification is not subject to the food additive premarket approval requirements of Section 409 of the Federal Food, Drug, and Cosmetic Act, based on the submitter's conclusion that Renmatix's maple fiber is GRAS under the conditions of its intended use.

1.7 Availability of Data and Information to FDA

Should FDA ask to see the data and information that are the basis for the submitter's conclusion of GRAS status, Ramboll and Renmatix will:

i) Agree to make the data and information available to FDA;

ii) Agree to the following procedures: Upon FDA's request, Ramboll and Renmatix will allow FDA to review and copy the data and information as provided in 21 CFR 170.225(c)(7) and upon FDA's request, we will provide FDA with a complete copy of the data and information either in an electronic format that is accessible for FDA's evaluation or on paper.

1.8 Freedom of Information Act (FOIA)

None of the data and information in Parts 3 through 7 of this GRAS notice is exempt from disclosure under the Freedom of Information Act, 5 U.S.C. 552.

1.9 Certifications

To the best of the knowledge of Renmatix and Ramboll, this GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to Ramboll and Renmatix and pertinent to the evaluation of the safety and GRAS status of the use of maple fiber in food.

1.10 Name(s) and Positions(s) of Signatories

Based on an evaluation of relevant data laid out within this report, the submitter has determined that Renmatix's maple fiber is safe for its intended uses and generally recognized as safe (GRAS) under the terms of 21 CFR § 170.30.

We have also concluded that other "experts qualified by scientific training and experience to evaluate the safety of food and food ingredients" would agree.

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

2.1 Scientific Data and Information that Identifies the Notified Substance

2.1.1 Substance Name, Origin, Composition, and Other Characteristic Properties

The subject of this GRAS evaluation is maple fiber, consisting primarily of cellulose and lignin, manufactured using Renmatix's Plantrose® process. Maple fiber, known commercially as Nouravant®, is produced in several forms. The typical composition of these forms is shown in Table 1.

Table 1. RENMATIX NOURAVANT® M*aple Fiber* Compositions

GRADE	FORM	COLOR	PROCESS	TOTAL SOLIDS	CELLULOSE	LIGNIN	Ratio (Cellulose:Lignin)	GLYCERIN	WATER
Nouravant® H1	Hydrate	Brown	Standard	17%	14.5%	2.5%	5.8:1	0	83%
Nouravant® H2	Hydrate	Tan	Caustic wash	15%	14.3%	0.7%	20.4:1	0	85%
Nouravant® P1	Powder	Brown	Standard Dewater	98%	66.7%	11.7%	5.8:1	19.6%	2%
Nouravant® P2	Powder	Tan	Caustic wash Dewater	98%	74.5%	3.9%	20.3:1	19.6%	2%

2.1.2 CAS Registry Numbers

The Chemical Abstracts Service Registry Number (CASRN) for cellulose is 9004-34-6 and for lignin is 9005-53-2.

2.1.3 Empirical and Structural Formulas

Cellulose is a polysaccharide consisting of a linear chain of several hundred to many thousands of β(1→4) linked D-glucose units. Cellulose is an important structural component of the primary cell wall of plants. It is the most abundant organic polymer on Earth – wood is about 50% cellulose and cotton is about 90% cellulose (Lehninger 1970; Encyclopedia Britannica https://www.britannica.com/science/cellulose). Its chemical formula is $(C_6H_{10}O_5)_n$.

The structure of cellulose is illustrated in Figure 1, below.

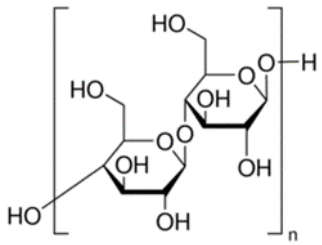

Figure 1. Cellulose Chemical Structure

Lignin is a three-dimensional (highly branched) polymer composed of phenol units with strong intramolecular bonding. A representative structure is shown in Figure 2.

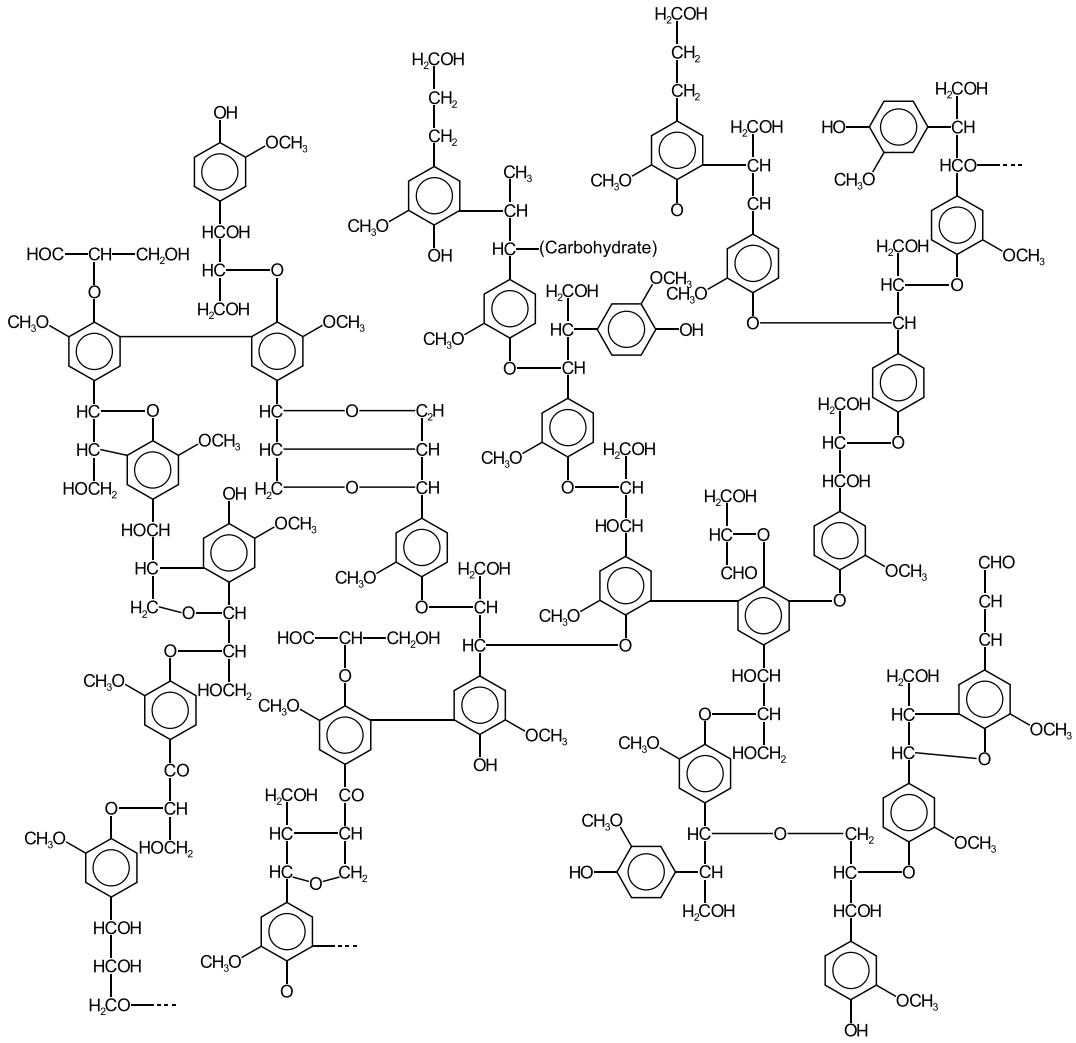

Figure 2. Example of Lignin Structure

The primary phenols that comprise lignin are coniferyl alcohol, trans-sinapyl alcohol, and trans-*p*-coumaryl alcohol, shown in Figure 3. These monomers differ only in the number of methoxyl groups. In softwoods, coniferyl alcohol is the dominant monomer (94% coniferyl, 1% sinapyl, 5% coumaryl alcohols). In hardwoods, both coniferyl and sinapyl alcohols are present in significant amounts, whereas grasses have large quantities of all three phenylpropylenes. The proportion of the different monomers varies widely in food plants. In a study by Bunzel et al. (2005) of 11 common fruits and vegetable, the ratio of coniferyl alcohol (guaiacyl residues) to sinapyl alcohol (syringyl residues) ranged from 39 in carrot to 0.2 in rhubarb, with coumaryl alcohol (*p*-hydroxyphenyl residues) not detected or detected in only trace amounts, except in small radish where it represented about 6% of the total. In this regard, the composition of the lignin in most edible fruits and vegetables is more like that of hardwoods than softwoods or grasses (Holtzapple 2003).

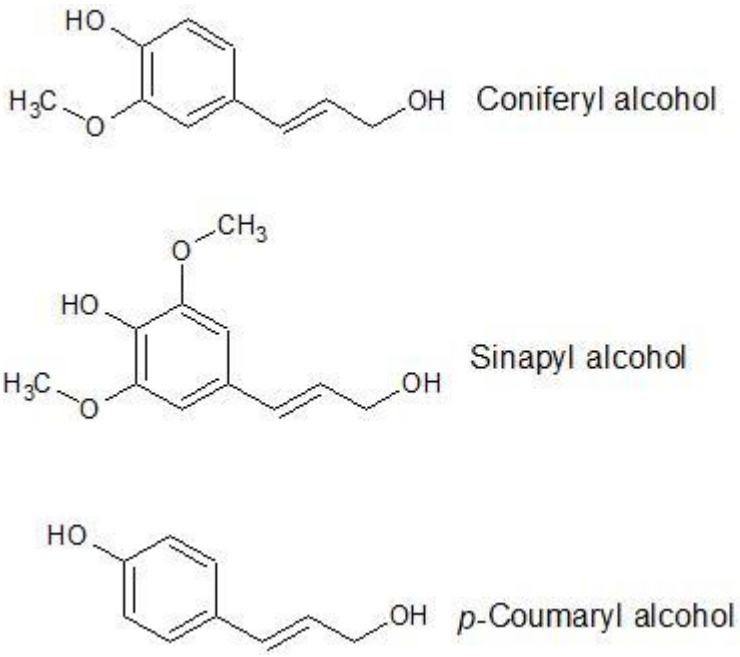

Figure 3. Primary Phenols in Lignin

Unlike other biological macromolecules, like DNA, RNA and protein, the structure of lignin is essentially random, with the three primary monomers incorporated at random, depending on their availability (Ralph et al. 2004). As a result, there is a very low probability of any two lignin molecules being identical, even in the same plant.

Lignin forms the structural components of plants and is thought to attach to plant polysaccharides forming a composite material known as "lignocellulose" found in plant cell walls (Holtzapple 2003). While lignin is most prevalent in woody plants, it is also found extensively in food plants, and forms an important component of dietary fiber (21 CFR 101.9(c)(6)(i)).

2.1.4 Characteristic Properties

Renmatix's maple fiber consists of particles of cellulose and lignin that are typically in the range of 0.5 to 2.5 µm in diameter (see Figure 7; Part 2.6).

2.2 Source and Description of Manufacture

Renmatix's maple fiber is produced from red maple (*Acer rubrum*) wood chips using a hydrothermal process developed by Renmatix. The base process includes the use of only water (with no added chemicals or solvents), and only the optional decolorization process uses caustic and acid as processing aids. All of the procedures used in the production of Renmatix's maple fiber comply with current Good Manufacturing Practice (cGMP) as laid out in 21 CFR 117.

Acer rubrum wood chips, which are free of pesticide residues and heavy metals, or other contaminants or natural components that are potentially harmful, are subjected to a series of processes, described below, that release cellulose and lignin from the wood and isolate it in a separate stream. The overall process is illustrated in Figure 4.

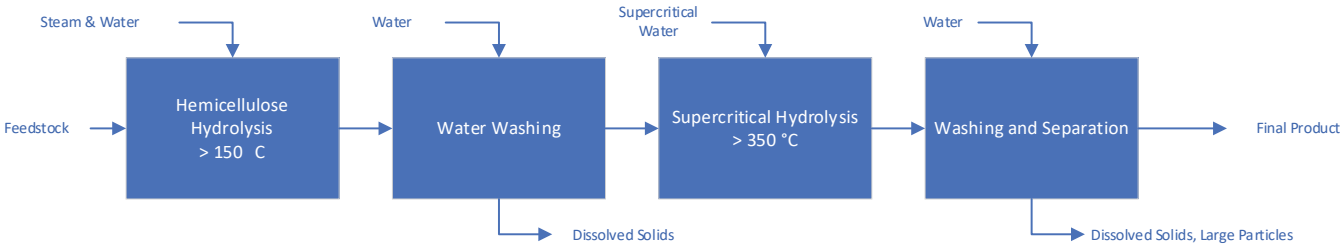

Figure 4 Flowchart for Supercritical Hydrolysis of Cellulosic Feedstocks

2.2.1 Hemicellulose Hydrolysis

First, biomass is conveyed into a digester, which uses steam and hot water under pressure to heat and soak the biomass. This causes the hemicellulose in the biomass to hydrolyze. The eventual reduction in pressure causes the hot pressurized water in the pores of the biomass to expand rapidly, causing the solids to break into a finer powder.

2.2.2 Water Washing

In this step, the material from the Hemicellulose Hydrolysis step is reslurried with water to remove any material that was previously dissolved with dewatering equipment (e.g., filters, centrifuges, etc.). The washed material is removed from this step as a moist solid. Currently, the solids produced are bagged in super-sacks and palletized for warehousing and shipment to the Supercritical Hydrolysis location. In the future, solids will move directly to the supercritical hydrolysis skid.

2.2.3 Supercritical Hydrolysis

In this step, the cellulose and lignin in the solid feed are physically separated in a chemical reaction using hot compressed water, while minimizing degradation of the cellulose byproducts in the liquid stream, and developing a clean cellulose/lignin stream with minimized thermal damage.

Currently, the super-sacks of water-washed Hemicellulose Hydrolysis solids are unloaded and conveyed to a mixing tank where they are mixed with water to form a thick slurry. The slurry is then pumped to a Supercritical Hydrolysis step. There, the slurry is mixed with supercritical and/or subcritical water at temperatures of 350-450°C.

2.2.4 Washing and Separation

The purpose of this step is to separate maple fiber product from other forms of product of the process. A series of gravimetric and filtration equipment are optionally used to remove any dissolved solids in a liquid stream and perform size separation. All steps are performed with water. The final product form is a hydrogel of solids and water with a solids content of 13-18.0 wt%.

2.2.5 Optional Decolorization Step

This optional step takes advantage of the solubility of lignin in caustic to reduce the overall lignin content in the product. The equipment elements of this process step are the same as the Washing and Separation step described above in 2.2.2, with the following exceptions:

1) Sodium hydroxide meeting the specification of the Food Chemicals Codex, 3rd Ed. (per 21 CFR 184.1763) is introduced as a processing aid to dissolve lignin;
2) Solubilized lignin and caustic is removed via washing (gravimetric and/or filtration); and
3) Sulfuric acid meeting the specification of the Food Chemicals Codex, 3rd Ed. (per 21 CFR 184.1095) is introduced as a processing aid to precipitate any remaining solubilized lignin and to neutralize the product back to its natural pH (neutralize any residual caustic).

This optional decolorization process is illustrated in Figure 5.

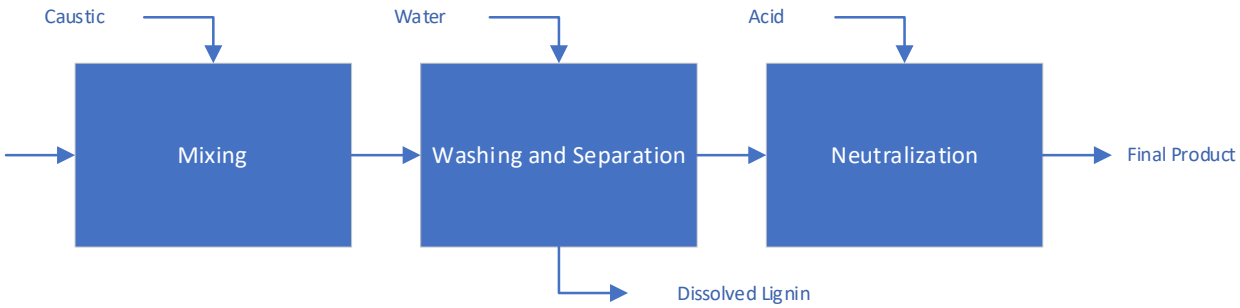

Figure 5. Optional Decolorization Process

The decolorized (reduced lignin) product contains 0-10% lignin; the regular product contains 5-25% lignin.

2.2.6 Finishing Process

The maple fiber gel is heated and held for sufficient time to pasteurize it. Optionally, preservatives acceptable for food can be added during heat treatment according to GMP, such preservatives could include cultured dextrose (up to 1 wt%) or a combination of sodium benzoate (21 CFR 184.1733) (up to 0.1 wt%) and potassium sorbate (21 CFR 184.3640) (up to 0.3 wt%) as examples. The pasteurized gel is hot-filled into a sealable container (See Figure 6). The pasteurized gel is passed through a size exclusion element to mitigate physical hazards.

Figure 6. Finishing Process

Important parameters to control in the process to maintain product quality on this finishing step are: the final concentration; the heat treatment fill time and temperature; and the size exclusion. The last of these (heat treatment time / temperature and size exclusion) are also HACCP Critical Control Points to ensure the safety of the product (biological and physical hazard perspective).

2.3 Specifications

Specifications for release of lots of Maple Fiber are shown in Table 2.

Table 2. Maple Fiber Release Specifications

Measurement	Procedure	Limit
pH	CORP-LAB-17101	3.0 – 4.0
PSD (d_{10})*	CORP-LAB-17102	$d_{10} \geq 0.3$ µm
WS-Carb* = % cellulose	CORP-LAB-17022	≥ 75%
Viscosity @ 2 rpm & temperature between 20°C and 30°C	CORP-LAB-17103	≥ 20,000 cP
Total Solids (TS)	CORP-LAB-17010	15-18 wt%
Dissolved Solids (DS)	CORP-LAB-17011	≤ 0.5 wt%
Total Aerobic Plate Count (APC)	AOAC 990.12	< 1000 CFU/g
Yeast and Mold	FDA BAM Chapter 18 or AOAC 997.02	< 100 CFU/g
Salmonella	AOAC 2003.09 or AOAC 2013.01	Non Detected / Negative
E. coli	FDA BAM Chapter 4 or AOAC 991.14, 998.08	Non Detected / Negative
Listeria	AOAC-RI 050903 or AOAC 2013.10	Non Detected / Negative
Arsenic – As	ICP	< 0.5 mg/kg
Cadmium – Cd	ICP	< 0.5 mg/kg
Lead – Pb	ICP	< 0.5 mg/kg
Mercury – Hg	ICP	< 0.1 mg/kg
*PSD = particle size distribution; WS-Carb is an indicator of cellulose separation in the Size Separation Step.		

2.4 Batch Analysis Results

Table 3 shows the results of analysis of six recent, non-consecutive lots of regular Nouravant® (H1) Maple Fiber. Similarly, results of analysis of six recent, non-consecutive lots of decolorized Nouravant® (H2) Maple Fiber are shown in Table 4. Both varieties show compliance with the specifications shown in Table 2

Table 3. Results of Analysis of Six Recent, Non-consecutive Batches of Nouravant® H1 Maple Fiber

Batch #	SC3-200409-0646	SC3-200416-0137	SC3-200505-0325	SC3-200505-1055	SC3-200508-1429	SC3-200511-1502
d_{10} (µm)	0.516	0.608	0.613	0.648	0.506	0.613
Cellulose (% TS)	76.7	81.5	72.2	72.2	76.5	80.9
DS (%)	0.259	0.260	0.177	0.180	0.196	0.251
TS (%)	17.7	16.8	16.2	16.3	16.2	17.0
Viscosity (cP) @ 2 rpm	51,900	40,930	38,790	39,590	31,030	27,290
As (mg/kg)	<0.002	<0.002	<0.01	<0.01	<0.01	<0.01
Cd (mg/kg)	<0.002	<0.002	<0.005	<0.005	<0.005	<0.005
Pb (mg/kg)	0.007	0.01	0.009	0.088	<0.008	0.008
Hg (mg/kg)	<0.003	<0.003	<0.005	<0.005	<0.005	<0.005
APC (cfu/g)	<10	<10	<10	<10	<10	<10
Yeast & Mold (cfu/g)	<10	<10	<10	<10	<10	<10

*E. c*oli (mpn/g)	<3	<3	<3	<3	<3	<3
Salmonella	Not Detected	Not detected	Not detected	Not detected	Not detected	Not detected
Listeria	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected	Not Detected

Table 4. Results of Analysis of Six Recent, Non-consecutive Batches of Nouravant® H2 Maple Fiber

Batch #	FM_200727-0857	FM-200804-FM-1242	FM-200812-0943	FM-200812-1238	FM-200813-0922	FM-200813-1304
d_{10} (µm)	0.449	0.398	0.428	0.502	0.428	0.430
Cellulose (% TS)	96.8	98.6	90.3	98.2	91.6	92.3
DS (%)	1.36	1.38	1.21	1.23	1.19	1.14
TS (%)	14.6	12.6	14.3	14.2	13.7	13.8
Viscosity (cP) @ 2 rpm	126780	59920	66880	61125	52160	52960
As (mg/kg)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Cd (mg/kg)	0.0501	0.0524	<0.05	<0.05	<0.05	<0.05
Pb (mg/kg)	0.13	0.14	0.115	0.121	0.085	0.0869
Hg (mg/kg)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
APC (cfu/g)	<10	<10	<10	<10	<10	<10
Yeast	<10	<10	<10	<10	<10	<10
Mold	<10	<10	<10	<10	<10	<10
E. Coli (mpn/g)	<3	<3	<3	<3	<3	<3
Salmonella	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
Listeria	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected

2.5 Analysis of Potential By-Products

Any hydrolysis of lignocellulosic biomass involves the breakdown, or degradation, of the biomass in a sequence of reactions. This sequence begins with the biomass, then to its constituent parts, then to reducing the length of the polymer chains of hemicellulose and cellulose to oligomers, then to monomer sugars and then further to byproducts. This breakdown process is similar to the cooking process of fruits and vegetables in a kitchen. The products of the breakdown of starch when heated have long been known (Bryce & Greenwood 1963). In the process described herein to make the maple fiber product, the water-soluble oligomer and monomer sugars as well as these byproducts leave the Supercritical Hydrolysis step (2.2.3) in the liquid stream. When making the maple fiber product, the conditions and reaction time are controlled to end the hydrolysis when an optimized amount of solid cellulose and lignin are produced while limiting the amount of solubilized sugars and byproducts.

Analyses have been made of the liquid stream from the Supercritical Hydrolysis step (2.2.3) to identify and measure the components that may have been produced during the hydrolysis reactions (other than the solid cellulose and lignin) that are contained in the liquid stream. Substances identified in the liquid stream include sugar oligomers, dimers (cellobiose), monomers (glucose, arabinose, xylose, mannose, fructose, and galactose), and various acids and other sugar breakdown products.

As described above (Part 2.2), after Supercritical Hydrolysis, this liquid stream is filtered and the solids are washed using water. As shown in the product specifications (see Table 2), Dissolved Solids are reduced in the process to lower than or equal to 0.5wt% in the final maple fiber product. Nothing other than water (and processing aids in the case of optional decolorization), are added or used in the processing through to the final product.

The identity and quantity of byproducts in the dissolved solids in the final product is discussed in Part 6.6, which also includes a discussion related to the safety of these byproducts.

2.6 Particle Size

The particle size distribution of 120 samples of Renmatix maple fiber was evaluated using a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer with Universal Liquid Module. Results were presented as mean, 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile particle diameters. These values were averaged over all 120 samples and the results are presented in Figure 7. The overall average median particle diameter was 0.91 µm, with an interquartile range of 0.69 to 1.26 µm. The full results of these tests are attached.

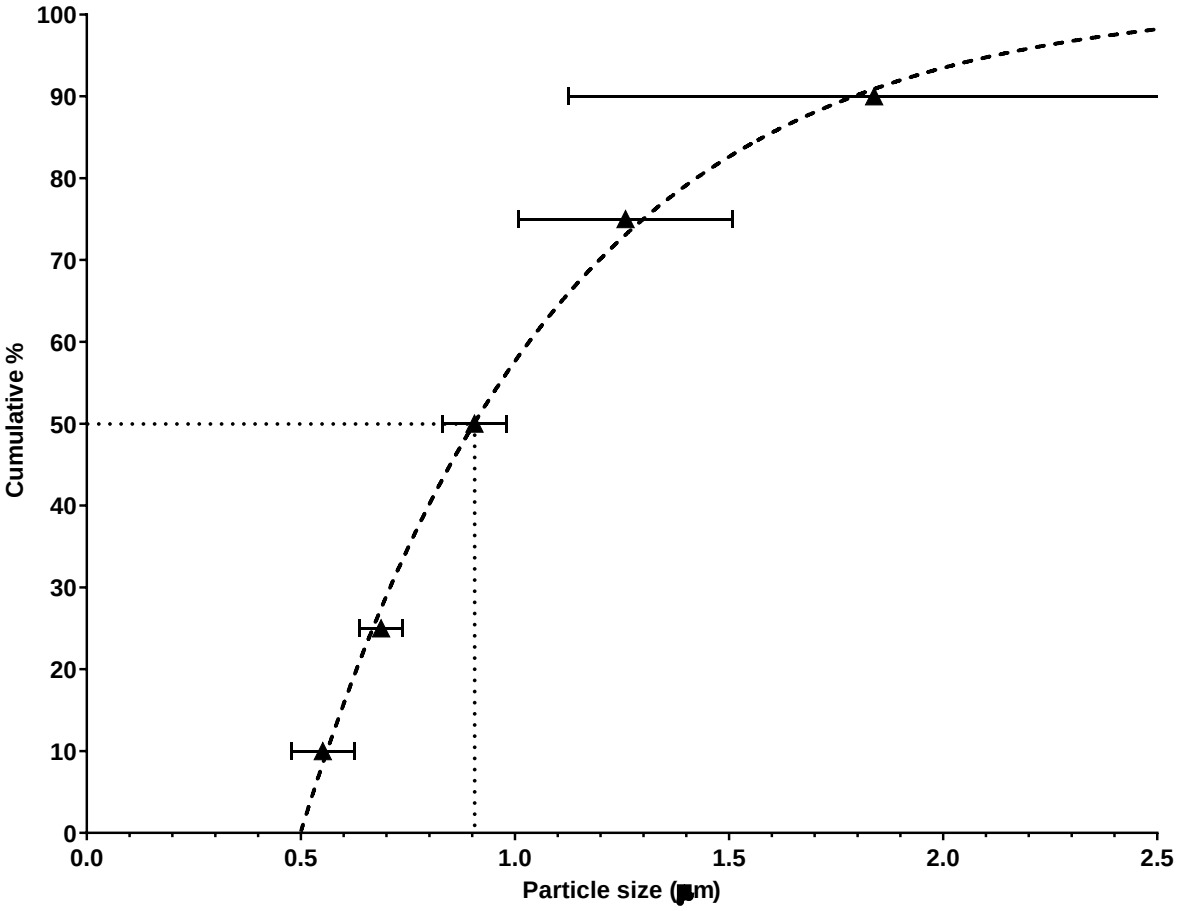

Figure 7. Average Particle Size Distribution of Nouravant® Maple Fiber (Based on Data from 120 Samples, outliers removed)

2.7 Impurities and Contaminants

Renmatix tested three batches of maple fiber for a suite of pesticides (4,4'-DDD, 4,4'-DDE, 4,4'-DDT, Aldrin, alpha-BHC, beta-BHC, Chlordane, delta-BHC, Dieldrin, Endosulfan I, Endosulfan II, Endosulfan sulfate, Endrin, Endrin aldehyde, Endrin ketone, gamma-BHC (Lindane), Heptachlor, Heptachlor epoxide, Methoxychlor, and Toxaphene). None were found in any sample at or above the detection limit (mostly 7.6, 8.6, or 15 µg/kg). The full testing results are attached.

As shown in T

.

Part 3. Dietary Exposure

Renmatix's maple fiber will be used in food largely as an alternative to microcrystalline cellulose, but may also replace texturizers such as xanthan or guar gum, and emulsifiers such as lecithin in some applications.

Estimates of potential intake of Renmatix product which contains maple fiber were calculated for the general US population, using consumption data reported in the Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Surveys (NHANES) for 2013-2014 and 2015-2016 (CDC 2019a, 2019b). NHANES is a multiyear program designed to assess the health and nutritional status of adults and children in the United States. The NHANES program includes interviews on demographics, socioeconomic, dietary and health-related questions with an examination program that consists of medical, dental, and physiological measurements. In the NHANES dietary section, a trained dietary interviewer collects detailed information about the food and beverages consumed by the respondents on the previous day – from midnight to midnight. A second dietary recall interview is administered by phone 3 to 10 days after the first interview and is scheduled to occur on a different day of the week than the first interview. For NHANES 2013-2014, a total of 8,661 individuals provided complete dietary intakes for the first interview and 7,574 of these individuals provided a complete day 2 dietary intake recall. For NHANES 2015-2016, a total of 8,506 individuals gave complete dietary intakes for the first interview and 7,027 of these provided complete dietary intakes for the second interview. These two sets of dietary data (NHANES 2013-2014 and NHANES 2015-2016) were combined for this analysis along with the physiological data of body weight in kilograms (kg). Since multiple surveys were used, the population weights assigned to these data were adjusted so that the combination was still a nationally representative sample of dietary intake. When combining two sets of NHANES data (such as 2013-2014 and 2015-2016) the weights that provide national representation must be divided by 2, as specified by the CDC in their documentation of the NHANES data (CDC 2018).

To determine the grams of specific products in the food that was eaten by the NHANES survey participants, data from the United States Department of Agriculture's Food and Nutrient Data base for Dietary Studies (FNNDS) were used (USDA 2016, 2018). A new version of this database in released with each 2-year NHANES dietary data set. The recipes available in the FNNDS database were used to determine the percentage of specific ingredients in a food to determine the percentage of a food item that belonged to a category of food being investigated.

3.1 Generation of the Special Split Values

The categorization of the potential foods was completed within the 'NHANES 2013-16 Food Codes' worksheet, and the selected foods of interest were merged with their respective ingredients using both years of the USDA's FNDDS Ingredients list. A complete list of the standard reference (SR) codes for the ingredients in food was generated, compiled into EXCEL, and specific SR codes which belonged to the desired categories were selected from within the food's listed ingredients. These SR codes were compiled into the worksheet 'Combined,' with their respective category and description. If a food was categorized as all belonging but its ingredients did not contain a readily utilized SR code or were not broken down by their ingredients, then food was place into the 'Combined' worksheet. During the procedure of the SAS analysis of the survey data, two output files were generated; one output contained the foods that were missing information on how to split them into their components and the other contained all the NHANES foods codes where the percentages of the categorized ingredients could be determined from the recipes.

The output file with the specific recipe information was then used to determine the best estimated value for those food codes for which specific ingredients had not been determined. The foods codes

were aligned with similar recipes, typically found for similar food codes, and were used as a reference to incorporate into these "special" split values.

3.2 Generation of the Consumption Data

On an individual basis, the amount of each food category consumed by a participant in the NHANES survey was then determined for each day of the survey. Totals were calculated on an individual basis as well. The amount of food consumed was then averaged over the two days of the survey, and finally divided by the individual's body weight to obtain a food consumption per category in mg/ kg of body weight/day. The amount of Renmatix product that would be consumed in that food considering the provided use levels and the amount of maple fiber consumed were determined by multiplying the estimates of use and maple fiber by category with the grams/kg BW/day of food consumed. Finally, survey statistics were used in SAS version 9.4 to determine the estimated average amounts of food, Renmatix product, and maple fiber consumed (using both a base and upper bound for Renmatix product and maple fiber) in the US population as specified in Table 4. This was done for all participants in the survey and for only those participants that consumed a food item. The latter choice gives estimates of the average amount of these food items eaten by consumers only and is the preferred choice for estimating the amount of maple fiber that would be consumed daily and is provided in Table 5.

All results and the data used in this method are provided in the Excel workbook entitled Renmatix Consumption Assessment 8-1-19.xlsx. The workbook contains the following sheets:

- Results All Survey Participants – these results included those who reported no consumption of a product (e.g. zeros were included in calculation of the means)
- Results Consumers Only – these results are for only those who reported eating the food category
- Categories – the categories that into which food items were combined and includes the percentages of use level, maple food solids, and upper bounds on both.
- NHANES 2013-16 Food Codes Used – all the NHANES codes used along with the categories to which the food was classified. Note that if the category code appears in the cat column, then 100% of the food goes into the category. If the categories fall into the recipies_0, recipes_1 or recipes_2 columns then the food was split into specific components that went into each category using the recipes or special splits.
- Special Splits – Since the recipes associated with the NHANES food codes are not complete (e.g. some are not broken down into their components), in these specific cases we have used our judgement to attribute a percentage of the food into the categories to which it is associated. The highlighted cells are indication of a food code that is split among two or more categories. The pct column show the fraction of the food that we attributed to the category. Where possible, similar recipes were used to determine these fractions (such as pie crust or breading).
- SRCODES by Category – these are the codes used in the recipes files which correspond to a category and are how all but the special splits are split among categories. Using the recipes, the percentage of each item in the recipe was determined and the amount of the ingredient(s) specified by these codes were added to the food consumed in the category to which it is associated.
- NHANES 2013-16 Food Codes Excluded – the list of food codes not allocated to any category.

Table 5. Usage Levels of the Renmatix Product by Food Categories

Categories				Renmatix Product Use Levels			
Major	**Description**	**Minor**	**Description**	**Use level (%)**	**Maple fiber solids (%)***	**Upper use Level (%)**	**Upper maple fiber solids (%)***
1	Bread & Bakery	A	Quick breads: muffins, pancake, crepes, etc.	4.6%	0.8%	9.1%	1.5%
		B	Allergen free quick breads	10.1%	1.7%	20.2%	3.4%
		C	Gluten free breads	5.5%	0.9%	11.0%	1.9%
		D	Brownie	5.0%	0.9%	10.0%	1.7%
		E	Low fat brownie	5.3%	0.9%	10.5%	1.8%
		F	Gluten free and/or vegan brownie	5.0%	0.9%	10.0%	1.7%
		G	Cake	5.3%	0.9%	10.5%	1.8%
		H	Layered cakes	5.5%	0.9%	11.0%	1.9%
		I	Leavened bread	5.6%	0.9%	11.1%	1.9%
		J	Gluten free leavened bread	5.6%	1.0%	11.2%	1.9%
		K	Cookie, various types	1.4%	0.2%	2.8%	0.5%
		L	Pretzels	4.0%	0.7%	8.0%	1.4%
		M	Brioche	7.6%	1.3%	15.2%	2.6%
		N	Donut, scratch, cake or leavened	1.4%	0.2%	2.8%	0.5%
		O	Donut, mixes, cake or leavened	1.8%	0.3%	3.6%	0.6%
		P	Dough: pies, pizza, uncooked cookie	3.0%	0.5%	6.0%	1.0%
		Q	Biscuits	1.5%	0.3%	3.0%	0.5%
2	Meat Systems	A	Sausage, traditional	5.8%	1.0%	11.7%	2.0%
		B	Sausage, poultry, 100% white meat (low fat)	5.8%	1.0%	11.7%	2.0%
		C	Hot dog	4.9%	0.8%	9.9%	1.7%
		D	Ground meat binder	2.0%	0.3%	4.1%	0.7%
		E	Plant protein, protein analogues: patties & forms	6.0%	1.0%	12.0%	2.0%
3	Sauces	A	Egg free mayo, mayo-based spreads, dips, dressings	10.0%	1.7%	20.1%	3.4%
		B	Tomato based sauces, ex. BBQ, marinara	2.0%	0.3%	3.9%	0.7%
4	Other	A	Pasta, fresh or dried, shaped or sheeted	7.0%	1.2%	14.0%	2.4%
		B	Flour tortillas, flatbreads	2.0%	0.3%	4.0%	0.7%
		C	Batters, coating, fried	3.4%	0.6%	6.8%	1.2%
		D	Granola, bark or seeds, bars	5.0%	0.9%	10.0%	1.7%
		E	Phyllo pastry, egg roll/dumping wrap and similar	3.0%	0.5%	6.0%	1.0%
4	Other	F	Margarine, emulsified spread	5.0%	0.9%	10.0%	1.7%
		G	Icing	8.0%	1.4%	16.0%	2.7%
		H	Confectionary	4.0%	0.7%	8.0%	1.4%
		I	Chocolate, chocolate products	3.0%	0.5%	6.0%	1.0%
		J	Nut butters, spreads	10.0%	1.7%	20.0%	3.4%
5	Dairy	A	Eggnog	7.8%	1.3%	15.6%	2.6%
		B	Yogurt culture based spreads, dips, dressings	17.0%	2.9%	34.0%	5.8%
		C	Non-dairy cream cheese spread, vegan	3.0%	0.5%	6.0%	1.0%
		D	Cheese, natural/synthetic processed	5.0%	0.9%	10.0%	1.7%
		E	Iced cream, gelato, frozen yogurt	10.5%	1.8%	21.0%	3.6%
		F	Cheesecake (filling only)	3.0%	0.5%	6.0%	1.0%
		G	Nutritional drink or shake	4.0%	0.7	6.0%	1.0
*Based on 17% solids in maple fiber							

Table 6. Consumption Levels by Users in g/kg Body Weight/day

Category				Sample Size (N)	Consumption of Food (g/kg BW/d)	Renmatix Product Consumption			
Major	**Description**	**Minor**	**Description**			**Use Level (g/kg BW/d)**	**maple fiber solids (g/kg BW/d)**	**Upper Use Level (g/kg BW/d)**	**Upper maple fiber solids (g/kg BW/d)**
1	Bread & Bakery	A	Quick breads: muffins, pancake, crepes, etc.	3666	1.7501	0.0796	0.0135	0.1593	0.0271
		B	Allergen free quick breads	-	n/a*	n/a	n/a	n/a	n/a
		C	Gluten free breads	49	1.2358	0.0680	0.0116	0.1359	0.0231
		D	Brownie	347	0.9706	0.0485	0.0082	0.0971	0.0165
		E	Low fat brownie	-	n/a	n/a	n/a	n/a	n/a
		F	Gluten free and/or vegan brownie	-	n/a	n/a	n/a	n/a	n/a
		G	Cake	550	1.7443	0.0916	0.0155	0.1832	0.0312
		H	Layered cakes	1427	1.8868	0.1038	0.0177	0.2075	0.0353
		I	Leavened bread	11435	1.2948	0.0720	0.0123	0.1440	0.0245
		J	Gluten free leavened bread	-	n/a	n/a	n/a	n/a	n/a
		K	Cookie, various types	5131	0.9067	0.0129	0.0022	0.0258	0.0044
		L	Pretzels	490	0.8147	0.0326	0.0055	0.0652	0.0111
		M	Brioche	8	0.9845	0.0746	0.0127	0.1493	0.0254
		N	Donut, scratch, cake or leavened	-	n/a	n/a	n/a	n/a	n/a
		O	Donut, mixes, cake or leavened	913	1.2304	0.0220	0.0037	0.0440	0.0075
		P	Dough: pies, pizza, uncooked cookie	3971	3.3526	0.1006	0.0171	0.2012	0.0342
		Q	Biscuits	1124	1.2228	0.0183	0.0032	0.0367	0.0062
			Total Bread and Bakery	14749	2.3532	0.2436	0.0412	0.4872	0.0830
2	Meat Systems	A	Sausage, traditional	3464	0.8563	0.0500	0.0085	0.1000	0.0170
		B	Sausage, poultry, 100% white meat (low fat)	395	1.8347	0.1071	0.0182	0.2143	0.0365
		C	Hot dog	1446	2.4487	0.1207	0.0206	0.2414	0.0411
		D	Ground meat binder	4567	1.6705	0.0339	0.0058	0.0678	0.0115
		E	Plant protein, protein analogues: patties & forms	170	1.6705	0.1002	0.0170	0.2005	0.0341
			Total Meat Systems	7992	1.6764	0.0571	0.0097	0.1143	0.0195
3	Sauces	A	Egg free mayo, mayo-based spreads, dips, dressings	6514	0.4393	0.0441	0.0075	0.0881	0.0150
		B	Tomato based sauces, ex. BBQ, marinara	6906	0.7659	0.0151	0.0025	0.0302	0.0051
			Total Sauces	10532	0.6880	0.0219	0.0037	0.0439	0.0075

Category				Sample Size (N)	Consumption of Food (g/kg BW/d)	Renmatix Product Consumption			
Major	**Description**	**Minor**	**Description**			**Use Level (g/kg BW/d)**	**maple fiber solids (g/kg BW/d)**	**Upper Use Level (g/kg BW/d)**	**Upper maple fiber solids (g/kg BW/d)**
4	Other	A	Pasta, fresh or dried, shaped or sheeted	5243	3.3640	0.2351	0.0400	0.4703	0.0801
		B	Flour tortillas, flatbreads	5447	1.4398	0.0289	0.0049	0.0579	0.0098
		C	Batters, coating, fried	2443	1.1992	0.0407	0.0070	0.0813	0.0138
		D	Granola, bark or seeds, bars	1534	1.2759	0.0638	0.0108	0.1276	0.0217
		E	Phyllo pastry, egg roll/dumping wrap and similar	828	2.1381	0.0641	0.0109	0.1283	0.0218
		F	Margarine, emulsified spread	1943	0.1423	0.0071	0.0012	0.0142	0.0024
		G	Icing	186	0.6012	0.0481	0.0082	0.0962	0.0164
		H	Confectionary	3385	0.5528	0.0221	0.0038	0.0442	0.0075
		I	Chocolate, chocolate products	549	0.4284	0.0129	0.0022	0.0257	0.0044
		J	Nut butters, spreads	2197	0.5516	0.0552	0.0094	0.1103	0.0188
			Total Other	13084	2.1356	0.1210	0.0205	0.2420	0.0412
5	Dairy	A	Eggnog	16	2.3547	0.1832	0.0311	0.3664	0.0624
		B	Yogurt culture based spreads, dips, dressings	1749	0.7222	0.1228	0.0209	0.2456	0.0417
		C	Non-dairy cream cheese spread, vegan	-	n/a	n/a	n/a	n/a	n/a
		D	Cheese, natural/synthetic processed	6865	0.6142	0.0307	0.0052	0.0614	0.0104
		E	Iced cream, gelato, frozen yogurt	3823	2.5045	0.2625	0.0446	0.5249	0.0892
		F	Cheesecake (filling only)	171	2.0512	0.0615	0.0105	0.1231	0.0209
		G	Nutritional drink or shake	247	5.5077	0.2203	0.0386	0.3305	0.0551
			Total Dairy	9822	1.5491	0.0884	0.0150	0.1768	0.0301
			Overall Total:	**16241**	**5.0474**	**0.2593**	**0.0441**	**0.5170**	**0.0879**

*n/a indicates no foods belonging to this category could be determined in the NHANES 2013-2016 Surveys

Based on the information presented in Table 5, the highest intake of maple fiber solids among users of food products in which it is proposed to be used will be 44 mg/kg bw/day at the most likely usage levels, or 88 mg/kg bw/day at the upper usage levels. Since the solids content of the standard maple fiber product is 81.5% cellulose and 18.5% lignin, for a 70 kg person, these exposure levels would correspond to intakes of 2,510 mg cellulose/day and 570 mg lignin/day at the expected use level, and 5,020 mg cellulose/day and 1,140 mg lignin/day at the upper use level.

Part 4. Self-Limiting Levels of Use

Very high levels of intake of some forms of dietary fiber, including cellulose, can cause gastrointestinal disturbance (flatulence, diarrhea, etc.) which may limit use, and there is some indication that this may interfere with absorption of dietary minerals, such as calcium, if mineral intake is limited (IOM 2005), but no significant health effects are expected at typical levels of intake. Introduction of Maple fiber is not expected to increase total dietary fiber intake to levels associated with such effects, and the production of these effects, if they occurred, would tend to limit usage.

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

The statutory basis for this notice is 21 CFR § 170.30(b): "General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information."

Given the statutory basis for this notice, Part 5 is not applicable to this GRAS notice, though it should be noted that cellulose and lignin, as common components of fruits and vegetables (as discussed in Part 6), have been major components of the human diet for eons.

Part 6. Narrative

6.1 Introduction

While produced by a somewhat different process than other types of plant fiber commonly used in food and identified as GRAS, such as carrot fiber (GRN 116), oat hull fiber (GRN 342), rice bran fiber (GRN 373), corn hull fiber (GRN 427), sugar beet fiber (GRN 430), rice hull fiber (GRN 478), insoluble fiber from citrus peel (GRN 541), or pecan shell fiber (GRN 646), Renmatix's maple fiber is chemically similar to those materials, being composed of cellulose and lignin, and is expected to be handled by the body in the same way, like a dietary fiber.

By definition, "dietary fiber" is a highly complex substance resistant to absorption and digestion in the small intestine, and eventually undergoes partial or complete fermentation in the large intestine (American Association of Cereal Chemists 2001). Further, given the complexity of dietary fiber, the fermentation potential within the large intestine may vary according to water solubility and chemical structure. For example, water-soluble dietary fiber (e.g., pectin, inulin, and ß-glucans) is more readily fermented, while water-insoluble dietary fiber (e.g., celluloses, hemicelluloses and lignin) is less readily fermented (Weickert & Pfeiffer 2008). Lignin in particular is neither digested nor fermented in the small and large bowel (Holloway et al. 1978), though a couple of more recent studies have suggested some limited metabolism by gut microbiota (Begum et al. 2004; Niemi et al. 2013). Within the large intestine, dietary fiber increases the viscosity and bulking of feces, contributing to the increased laxation experienced with dietary fiber consumption (Simpson & Campbell 2015).

6.2 Safety Assessment Based on Analogy to other Cellulose- and Lignin-containing Plant Fibers

As noted in Part 2, above, the components of maple fiber, cellulose and lignin, are major components, along with hemicellulose, of the cell walls of all terrestrial plants, including food plants. For example, Southgate et al. (1969) reported the relative proportion of these three polymers in the cell walls of various food plants (Table 6).

Table 7. Composition of Cell-Wall Polymers in Food (g/100g) (Southgate et al. 1986)

Constituent	Wheat	Rye	Cabbage	Pea	Potato	Apple	Plantain
Hemicellulose	65.0	77.7	24.3	29.4	32.1	32.3	83.9
Cellulose	10.0	12.4	69.1	63.7	35.8	41.9	13.6
Lignin	23.3	9.9	6.4	6.9	32.0	24.8	2.1

Southgate et al. (1969) also reported the cellulose and lignin content of these foods as a percentage of the total food (Table 7).

Table 8. Cellulose and Lignin as Percent of Whole Foods (Southgate et al. 1986)

Constituent	Wheat Flour	Rye Flour	Cabbage (Cooked)	Peas (Cooked)	Potato (Cooked)	Apple	Plantain
Cellulose	1.1%	1.8%	0.81%	3.06%	0.35%	0.67%	1.0%
Lignin	2.6%	1.4%	0.08%	0.33%	0.31%	0.4%	0.2%

While the cellulose and lignin content of these foods is fairly low (0.6 – 3%, combined), the presence of cellulose and lignin in these foods at these levels is clearly safe, based on their long history of consumption. Moreover, the low levels of cellulose and lignin in these foods are comparable to the combined levels of cellulose and lignin proposed to be added to foods as shown in Table 4, where the typical total maple fiber solids addition levels are in the range of 0.2% to 2.7%.

Further support for the safety of mixtures of cellulose and lignin comes from the GRAS status of a number of other plant fiber materials that have received "no-questions" letters in response to GRAS notices over the past few years. The cellulose and lignin contents of these materials are shown in Table 8.

Table 9. Cellulose and Lignin Content of Plant Fiber Products Identified as GRAS

GRAS Notice (GRN#)	Product	Cellulose (%)	Lignin (%)	Uses
116	Carrot fiber	12.8%	11.4%	As a binder/extender and to reduce water purging and gelling in specific standardized and non-standardized meat and poultry products at use levels ranging from 0.4% to 5.0%
342	Oat hull fiber	70%	5%	As a food ingredient in meat and poultry at levels of 3.5% to improve the texture, control moisture migration, and improve stability of the food product
373	Rice bran fiber	42.3%*	27%	General food use at concentrations consistent with cGMP, including prepared foods, nutraceuticals, functional foods, general foods (such as snack foods, bakery products, cereals, crackers, pasta products, dough conditioners, beverages, sports beverages), meal replacement, gluten-free foods, and medical foods at levels up to 5-10% in beverages and some bakery products and 25% in ready-to-eat cereals
430	Sugar beet fiber	19%	2%	As an anticaking agent; binding agent; bulking agent; dispersing agent; source of dietary fiber; stabilizing agent; texturizing agent; or as a thickening agent for most uses at 1-3% of the food product; 1-5% for bread products, 1-10% for cereals and muesli, and 1-5% for meat products.
478	Rice hull fiber	49%	17%	General food use at concentrations consistent with cGMP at levels up to 5-10% in beverages and some bakery products and 25% in ready-to-eat cereals (specific purposes not reported)
541	Insoluble fiber from citrus peel	67%	13%	For use in baked goods, pastas, salad dressings, confectionery, processed cheese spreads, frozen food entrees, and comminuted and whole muscle meat and poultry products at a maximum level of 5%; in non-carbonated beverages and fruit drinks; in brine for use in comminuted and whole muscle meat and poultry products, and in salads, sauces, meats, fillings, dips, baked goods, dairy products, fruit-and vegetable-based products, and pizza products at a maximum level of 5% for use as a moisture retention agent, flavor enhancing agent, and processing aid.
646	Pecan shell fiber	49.7%	19.5%	In baked goods and baking mixes (2-5%), breakfast cereals (5%), confections and frostings (5%), gelatins, puddings and fillings (5%), grain products and pastas (2%), meal replacement (10%), snack food (2%), soft candy (10%), sweet sauces (5%).
*In GRN 373, rice fiber was reported to contain 42.3% "glucose," presumably in polymeric form, largely in the form of cellulose.				

As indicated in Table 9, these GRAS plant fiber products contain levels of cellulose (up to 70%) and lignin (up to 27%) that vary from product to product, but fall in a range that is comparable to that in standard (H1 grade) maple fiber (up to 81.5% total solids as cellulose, and up to 18.5% total solids as lignin). These GRAS plant fiber products are also used in similar types of food products at similar addition levels, on a total solids basis – the uses and usage levels reported in Table 9 (taken from the corresponding GRN) are similar to those for maple fiber solids reported in Table 5.

Based on the similarities between the composition of these GRAS mixed plant fibers and that of maple fiber, and the similarities in usage levels in food products, we conclude that the proposed uses of maple fiber in foods are also safe.

6.2.1 Safety Assessment Based on Pecan Shell Fiber (GRN 646)[1]

Of the various plant fiber products mentioned above, perhaps the most relevant to maple fiber is pecan shell fiber, since that is also derived from a hardwood tree, and is derived from material (pecan shells) that does not normally form part of the human diet. Like maple fiber, the primary components of pecan shell fiber identified in GRN 646 are cellulose (49.7%) and lignin (19.5%), with smaller amounts of moisture (6.45%), hemicellulose (4.9%), fat (4.2%), protein (2.53%), and ash (2.29%).

To support the safety of pecan shell fiber, Dolan et al (2016) reported results of a subchronic oral toxicity study in rats feed diets containing pecan shell fiber at 0, 50,000, 100,000, or 150,000 ppm, a bacterial reverse mutation assay in *S. typhimurium* and *E. coli* at doses up to 5,000 µg/plate (limited by precipitation of test material at concentrations of 1,000 µg/plate and higher, and some toxicity in strain TA1537), and a mouse micronucleus study in which male and female mice received pecan shell fiber suspended in cottonseed oil three-times/day for a total daily dose of 10 g/kg bw/day.

In the subchronic toxicity study, there was no effect of the ingredient on body weight of males or females or food consumption of females. Statistically significant increases in food consumption were observed throughout the study in mid- and high-dose males, resulting in intermittent decreases in food efficiency (high-dose males only) that were not considered biologically relevant. All animals survived and no adverse clinical signs or functional changes were attributable to the test material. There were no toxicologically relevant changes in hematology, clinical chemistry or urinalysis parameters or organ weights in rats ingesting pecan shell fiber. No significant macroscopic or microscopic findings were found that were attributable to the test substance. All microscopic findings occurred sporadically or at a similar incidence in control and treated groups and were of the type commonly seen in rats of this strain and age, and were, therefore, considered incidental and unrelated to treatment (Dolan et al. 2016).

The highest dietary concentration (150,000 ppm) was identified as a NOAEL, and corresponded to a mean overall intake of approximately 9,950 mg/kg bw/day in males and 11,100 mg/kg bw/day in females (Dolan et al. 2016).

Pecan shell fiber was not mutagenic in the bacterial reverse mutation test in any strain of *S. typhimurium* or *E. coli*, with or without metabolic activation, and was not clastogenic in a mouse peripheral blood micronucleus test (Dolan et al. 2016).

Given their similarity in composition (predominantly cellulose and lignin), maple fiber is expected to be similarly non-toxic like pecan shell fiber.

[1] Dossier in Support of the Generally Recognized as Safe (GRAS) Status of Pecan Shell Fiber as a Food Ingredient. January 29, 2016. GRN 646. Available at https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices

6.3 Safety Assessment of Cellulose

Cellulose is the most common natural polymer in the world, and is a major component, along with hemicellulose and lignin, of plant cell walls.

Because the cellulose component of Renmatix's maple fiber is chemically identical to cellulose, and is similar in particle size to microcrystalline cellulose, or cellulose gel, or slightly smaller than those forms of cellulose, we rely substantially on safety data for those materials to support the safety of maple fiber. Microcrystalline cellulose was evaluated at the fifteenth, seventeenth, nineteenth, and 49th meetings of the Joint Expert Committee on Food Additives (JECFA 1998a). At the nineteenth meeting, an ADI "not specified" was allocated due to the absence of safety concerns at foreseeable levels of exposure. In the light of concern about possible persorption (the passage of solid microparticles through the lining of the intestine) and potential adverse effects of fine particles, the substance was reevaluated at the 49th meeting.

JECFA (1998a) noted that in early studies, persorption of microcrystalline cellulose was reported in various species including rats. However, JECFA also cited a more recent study in which a special preparation of fine particle size microcrystalline cellulose (median diameter 6 µm) was administered orally to rats (0.5, 2.5, and 5 g/kg of body weight per day) for 90 days. This study failed to confirm the earlier observations (Kotkoskie *et al.* 1996). In this study precautions were taken to ensure that there was no cross-contamination of the tissues with fine particulate matter at autopsy, and no evidence of cellulose particles within the tissues of the animals was seen. In addition, no toxicologically significant effects on food consumption, ophthalmoscopic examinations, clinical chemistry measurements, hematology measurements, or absolute and relative organ weights were seen in animals receiving microcrystalline cellulose at up to 5 g/kg bw/day. No treatment-related lesions were found in any organ evaluated, and there were no macroscopic or microscopic findings of microemboli or granulomatous inflammation in any tissue, including the liver, lung, brain, spleen, intestinal wall and gut-associated lymphoid tissue (GALT).

Since no precautions to avoid cross-contamination were taken in the earlier studies cited by JECFA (1998a), it is likely that the identification of cellulose particles within the tissues that those studies reported was an artifact of the histology processing in those earlier studies.

In rats given microcrystalline cellulose intraperitoneally at 1,000 or 3,160 mg/kg, there were signs consistent with a tissue response to foreign particles (Pallotta 1959, as cited in JECFA 1998a). Similarly, microcrystalline cellulose has been associated with the formation of granulomas in human lung when it has been injected intravenously by drug abusers, but no such lesions have been described as a consequence of oral ingestion of microcrystalline cellulose by rats or humans (JECFA 1998a).

In 90-day toxicity tests during which microcrystalline cellulose was administered to rats at concentrations of 25 g/kg or 50 g/kg in the diet, increased consumption of food to compensate for the low energy content of this material was observed (Freeman et al. 1992a, 1994a, both as cited by JECFA 1998a). Although this may have some adverse effects on mineral absorption there was, in general, no compound-related systemic toxicity. The NOAEL was the high dose, 50 g/kg in the diet, equal to 3.8 g/kg of body weight per day in males and 4.4 g/kg bw/day in females (JECFA 1998a).

JECFA (1998a) reported that the execution and reporting of a 2-year study in rats were not adequate to identify a NOEL. A substantial battery of *in vitro* and *in vivo* genotoxicity studies was negative (JECFA 1998a). This included reverse mutation assays in *S. typhimurium* and *E. coli*, forward mutation assays in mouse lymphoma cells (L5178Y) in vitro, an unscheduled DNA synthesis assay in primary rat liver cells, and three in vivo mouse micronucleus assays.

In a 3-generation reproductive toxicity study in rats (Hazleton Labs, 1964, as cited by JECFA 1998a), there were some effects in animals given microcrystalline cellulose at 300 g/kg in the diet; these were considered to be a consequence of the quantity of material reducing the energy density of the diet, and not a direct toxic effect of cellulose. In embryotoxicity and teratogenicity studies in rats, there was no evidence of treatment-related effects at levels of up to 50 g/kg in the diet (equal to 4.6 g/kg of body weight per day), given on days 6 to 15 of pregnancy (Freeman 1992b, 1994b, as cited in JECFA 1998a).

In some studies in humans ingesting microcrystalline cellulose at 15-40 g/day, there have been reports of alterations in gastrointestinal function (JECFA 1998a). The changes do not appear to be related to systemic toxicity, but likely reflect the common effect of poorly digested carbohydrates, which can cause osmotic and fermentative effects in the colon, leading to diarrhea, flatus, etc. when ingested in large amounts (see Part 4).

Overall, JECFA (1998a) concluded that the toxicological data from humans and animals provided no evidence that the ingestion of microcrystalline cellulose can cause toxic effects in humans when used in foods according to good manufacturing practice.

In its evaluation, JECFA (1998a) identified NOAELs in the range of 3.8 to 4.6 g/kg bw/day in rodents (Freeman et al. 1992a, as cited in JECFA 1998a). In comparison, the maximum estimated human intake of maple fiber shown in Table 6, above, is 0.0915 g/kg bw/day, more than 40-times lower. Because of the lack of evidence for adverse effects from ingestion of microcrystalline cellulose, JECFA assigned an ADI of "not specified" to microcrystalline cellulose.

Because the particle size of the Renmatix Maple Fiber is smaller than normal microcrystalline cellulose, information on the safety of cellulose nanomaterials may also be relevant, though as illustrated in Part 2.6 the Renmatix maple fiber is not as small as "nanocellulose."

6.3.1 Nanocellulose data

As with many other materials, there has been interest in the use of cellulose particles at the nano-scale, and various forms of nanocellulose have been tested for safety in a variety of test systems. While there is some limited data suggesting that cellulose nanoparticles may present some health risk if inhaled (Yanamala et al. 2014; Catalan et al. 2017), ingestion of cellulose nanoparticles does not appear to present any health risk.

Pitkanen (2010, 2014) reported the results of *in vitro* cytotoxicity and genotoxicity testing of two forms of nanocellulose, a fibrillar form with long curly fibrils , typically 20-60 nm in diameter, and several µm long, and whisker-like short fibers. Cytotoxicity was tested in mouse hepatoma calls (Hepa-1c7c), human keratinocytes (HaCat), and human cervix carcinoma cells (HeLa229). The two forms of nanocellulose showed no evidence of cytotoxicity in these cells, as measured by morphology, total protein synthesis, or RNA synthesis inhibition, while the positive control (dinitrophenol) produced the expected inhibition of protein synthesis.

The cytotoxicity of several nanocellulose preparations from various sources has been investigated by several researchers using a variety of test systems, including human brain microvascular endothelial cells, human gingival fibroblasts, human monocyte derived macrophages, human bronchial epithelial cells, human corneal epithelia cells, human colon cancer cells (HCT116), Chinese hamster V79 lung fibroblasts, mouse L929 cells, NIH 3T3 cells, and rainbow trout hepatocytes. The results of these studies have been summarized by Roman (2015). Most of these studies reported a lack of cytotoxicity, though a few reported toxic effects at high concentrations. The preparations used in these studies were prepared by strong acid hydrolysis of cotton or wood pulp, and these studies did not consider the possibly acidic nature of these preparations, which may have affected the results

(Roman 2015). Because Renmatix maple fiber does not use acid in its production these results are not relevant to it.

O'Connor et al. (2014) studied the acute and subchronic oral toxicity of cellulose nanocrystals according to OECD test guidelines 425 and 407. Acute oral toxicity was assessed by gavage administration of one-time doses of up to 2,000 mg/kg in aqueous suspension in Crl:CD(SD)BR rats and monitoring of the health of the rats for a period of 14 days. Using the same rat strain, the repeated-dose test was performed by daily gavage administration of doses of 500, 1,000, and 2,000 mg/kg/day for 28 days. During this period, the animals were closely observed for signs of toxicity. At the end of the test, all animals were subjected to gross necropsy. No adverse effects were observed in either study, and the median lethal dose was greater than the highest dose tested, 2,000 mg/kg. O'Connor et al. (2014) also reported the results of an acute inhalation toxicity study in rats, in which no mortality or signs of gross toxicity, adverse effects, abnormal behaviors or abnormalities were seen at the maximum attainable test concentration of 0.26 mg/l. In addition, cellulose nanocrystals were not irritating to the skin, and caused no signs of skin sensitization in OECD tests 406 and 429 (local lymph node assay). The material was not mutagenic up to the maximum concentration tested of 5 mg/plate in the bacterial reverse mutation assay (OECD 471), did not induce chromosome aberration in cultured Chinese hamster ovary cells at a maximum test concentration of 5 mg/ml (OECD 473), and did not induce micronuclei in the mouse micronucleus test at a maximum tested dose of 2000 mg/kg (OECD 474) (O'Connor et al. 2014).

6.4 Safety Assessment of Lignin

Lignin is a highly branched polymer that forms part of the primary cell wall of plants. While lignin is most prevalent in woody plants, it is also found extensively in food plants, and forms an important component of dietary fiber (21 CFR 101.9(c)(6)(i)).

As noted in Section 2.1.3, lignin is formed from three primary monomers, *trans*-coniferyl alcohol, *trans*-sinapyl alcohol and *trans-p*-coumaryl alcohol, that are found in different proportions in different plants. These three monomers differ only in the number of methoxy groups (-OCH_3) attached to the phenyl ring – one in coniferyl alcohol, two in sinapyl alcohol, and none in coumaryl alcohol. In softwoods, coniferyl alcohol is the dominant monomer (94% coniferyl, 1% sinapyl, 5% coumaryl alcohols). In hardwoods, both coniferyl and sinapyl alcohols are present in significant amounts, whereas grasses have large quantities of all three phenylpropylenes (Holtzapple 2003). Like in hardwoods, lignin in fruits and vegetables also contains substantial amounts of coniferyl and sinapyl alcohols, but very little coumaryl alcohol, except in small radishes (Bunzel et al. 2005). The safety of lignin does not seem to be affected by the proportions of the different monomers, since different species of commonly eaten fruits and vegetables contain very different ratios of these monomers (Bunzel et al. 2005; Bunzel & Ralph 2006), and that variation does not affect the safety of the fruits and vegetables. This is not surprising since ingested lignin passes through the digestive tract unchanged (Holloway et al. 1978), and without being absorbed.

In food plants, lignin is found especially in the stems and seeds of fruits and vegetables and in the bran layer of cereals. Examples of foods high in lignin include wheat, mature root vegetables such as carrots, and fruits with edible seeds such as many berries (Gropper et al. 2018). Table 9 lists some examples of lignin content of commonly eaten fruits and vegetables.

Table 10. Lignin Content of Some Foods

Food	Lignin	Reference
Chickpeas	0.73±0.10 (% dry weight)	Pérez-Hidalgo et al. (1997)
Kidney beans	1.11±0.18 (% dry weight)	
Lentils	1.45±0.10 (% dry weight)	
Chinese quince	2.1 ± 0.02 (% fresh weight)	Hamauzu & Mizuno (2011)
Quince	0.81 ± 0.01 (% fresh weight)	
Apple	0.02 ± 0.002 (% fresh weight)	
Pear (ripe)	0.40 ± 0.01 (% fresh weight)	
Blueberry (ripe)	0.73 ± 0.007 (% fresh weight)	
Whole wheat flour	0.9-1.0[a] (% dry weight)	Flint & Camire (1992)
Rice bran	4.5-5.3 [a] (% dry weight)	
Broccoli	2.1±0.6 (% dry weight)	
Pear (fresh)	1.3-1.4 [a] (% dry weight)	
Pear (canned)	1.8-1.9 [a] (% dry weight)	
All-Bran	2.8-3.3 [a] (% dry weight)	
Sunchips	0.7-1.8 [a] (% dry weight)	
Wheat bread	1.9-3.5 [a] (% dry weight)	
Wheat bran	4.0-7.0[a] (% dry weight)	
Orange pulp	2.2-3.0 (% dry weight)	Grigelmo-Miguel & Martin-Belloso (1999)
[a] Range of mean values from two analysis methods (permanganate lignin & Klason lignin)		

Even higher levels of lignin are reported in fruit pomace, the fruit solids remaining after pressing for juice (Nawirska & Kwasniewska 2005). These authors reported apple, cherry, chokeberry, black currant, pear, and carrot pomace as containing 20.4, 69.4, 24.1, 59.3, 33.5, and 32.2% lignin, respectively.

Holloway et al. (1978) reported lignin content of a variety of foods as eaten (Table 10).

Table 11. Lignin Content of Foods (as Eaten)

Food	Lignin (g/100 g edible portion)
Cornflakes	0.85
Bread	0.1
Tomato	0.39
Apple	0.02
Arrowroot biscuits	0.20
Potato	Trace
Carrots	0.04
Beans	0.11
Peas	Trace
Peaches	0.07
Sao cracker	0.50

Mongeau and Brooks (2001) summarize extensive data on the lignin content of a wide variety of fruits, vegetables, cereals, and other foods, with levels up to 27.9% in cocoa powder and 5.5% in wheat bran. Mongeau and Brooks (2001) note that lignin intake is approximately 13% of total dietary fiber.

Humans have been eating lignin as a natural component of the diet for millennia with no evidence of adverse health effects. In fact, there are data suggesting that lignins and their derivatives, like other dietary fibers, have beneficial effects on health (Vinardell & Mitjans 2017).

Both of the components of maple fiber, cellulose and lignin, are a natural part of dietary fiber (IOM 2001, 2005; FDA 2018). In its report on dietary reference intakes (DRIs) for fiber, IOM (2005) identified an Adequate Intake (AI) of dietary fiber as 38 g/day for men and 25 g/day for women, but noted that "median Dietary Fiber intakes ranged from 16.5 to 17.9 g/d for men and 12.1 to 13.8 g/d for women," substantially below what IOM concluded was an adequate intake. Not only would the estimated intake level of maple fiber not present a health risk to consumers, it would go some way towards moving the daily intake of fiber by the general population towards the IOM's recommended Adequate Intake. Furthermore, in its review, IOM (2005) concluded that "as part of an overall healthy diet, a high intake of Dietary Fiber will not produce significant deleterious effects in healthy people. Therefore, a Tolerable Upper Intake Level (UL) is not set for Dietary Fiber." Similarly, based on the lack of adverse effects associated with consumption of high levels of chemically similar materials, described above, no UL or ADI appears to be necessary for maple fiber.

6.5 Potentially Toxic Components of Wood

The European Food Safety Authority (EFSA 2019) recently published an update of the risk assessment of "*wood flour and fibres, untreated*" (FCM No 96) for use in food contact materials. In this document, EFSA discussed the possibility of toxic materials migrating from wood fiber to food, and pointed to the existence of known toxicants found in wood from various species of tree. They specifically identified the following species as containing toxic components: White Peroba, Lapacho, Pau d'arco, Teheebo, Ipo roxo, Cypress family (i.e. cedars, pines and junipers), Prunus spp. (i.e. red cherry, choke cherry, apricot, peach and plum), Juglulandaceae sp. (i.e. American black walnut, hickory (Pecan) and butternut), Quercus sp. (i.e. red, white and black oaks), Black locust, Dalbergia spp. (i.e. Kingwood, Sissoo, African blackwood, tulipwoods and rosewoods), Cocobolo, Pteorcarpus sp. (i.e. red sandalwood), Taxus spp. (i.e. English yew), Yellow poplar. Renmatix does not intend to use any of these species in its products. Maple has been used in food-contact uses (cutting boards, bowls, spoons, etc., for hundreds of years, with no reports of adverse health effects. Furthermore, the high-temperature and high-pressure water/steam treatments used in the production of maple fiber would remove any low-molecular-weight toxicants of the types found in wood of those other species. No such toxic substances occur in maple fiber produced by Renmatix.

6.6 Safety of Potential By-Products

As discussed in Part 2.5, any hydrolysis of lignocellulosic biomass involves the breakdown, or degradation, of the biomass in a sequence of reactions. In particular, hydrolysis of cellulose and hemicellulose results in the release of (depending on the type and length of the hydrolysis reaction) varying amounts of short oligomers and sugar monomers, some of which can subsequently break down further into various acids and other breakdown products. These same products are produced during the cooking of fruits and vegetables, and during the production of GRAS substances, such as caramel (Licht et al. 1992; Kroh 1994; Vollmuth 2018), polydextrose (Flood et al. 2004),and resistant dextrin (GRN 436). The safety of these byproducts in the context of caramel colors has been extensively reviewed by FDA (21 CFR 73.85, 21 CFR 182.1235), the Life Sciences Research Office's Select Committee on GRAS Substances (SCOGS, LSRO 1973), the Joint Expert Committee on Food Additives (JECFA 1987, 2003), and the European Food Safety Authority (EFSA 2011).

Based on analysis of multiple lots of maple fiber, few potential breakdown products were detected in the remaining dissolved solids in maple fiber. Table 11 shows the estimated daily consumption of these potential breakdown products, based on the estimates of maple fiber solids consumption derived

in Part 3 (Table 5), together with the relative concentration of the potential breakdown products found in multiple lots of the product.

The safety of these minor components of maple fiber at their estimated intake level from the uses described in Part 3 is discussed below.

Table 12. Estimated Daily Consumption of Maple Fiber Components (mg/kg bw/day)

Maple Fiber Component	Normal Usage	Upper-Level Usage
Maple Fiber Solids (Cellulose & Lignin) [a]	44.1	87.9
Oligomer and Monomer		
Oligomer	0.690	1.38
Glucose	0.050	0.099
Byproducts		
Formic Acid	0.049	0.098
Acetic Acid	0.0281	0.0560
Glycolic Acid	0.0215	0.0429
Glyceraldehyde	0.0040	0.0080
Levulinic Acid	0.0024	0.0048
[a] From Table 6, Part 3.2		

6.6.1 Oligomer

Sugar oligomers are common ingredients of the human diet, resulting from partial breakdown of starch and cellulose. When, as in this case, the oligomers are derived from cellulose, the β(1→4) glycosidic bonds between the glucose residues are resistant to mammalian digestive enzymes, and the intact oligomers are too large to be absorbed by the intestines. As a result, they pass through the digestive tract unchanged, though a small proportion may be degraded by the lower gut microbiota, releasing beneficial volatile fatty acids.

6.6.2 Glucose

Glucose is the primary metabolic fuel for humans. Except in individuals suffering from diabetes, glucose is not a safety concern, and the very low concentration of glucose in maple fiber presents no health risk to consumers.

6.6.3 Safety of Other Byproducts

Except where otherwise indicated, the following information is taken largely from Fenaroli's Handbook of Flavor Ingredients, 6th Edition, by George A. Burdock (2009).

6.6.3.1 Acetic Acid

Acetic acid is the characteristic acid of vinegar, its concentration ranging from 3.5 to 5.6%. Acetic acid and acetates are present in most plants and animal tissues in small but detectable amounts. They are normal metabolic intermediates. The rat forms acetate at the rate of 1% of its body weight per day.

It is useful in butter, cheese, grape and fruit flavors, and it is classified by FDA as GRAS as a curing and pickling agent; flavor enhancer; flavoring agent and adjuvant; pH control agent; as a solvent and vehicle; and as a boiler water additive (21 CFR 184.1005).

The WHO/FAO Joint Expert Committee on Food Additives (JECFA 1998b) has assigned an ADI of "not limited" to acetic acid because of its low toxicity.

Acetic acid has low acute toxicity, with a lethal dose in rats and mice of more than 3 g/kg bw. Its toxic effects are largely related to its low pH at high concentrations, though large oral doses cause narcotic CNS depression and death in rats and mice (Woodard et al. 1941, as reported by JECFA 1998b).

In short term toxicity studies, groups of three to six rats were given 0.01, 0.1, 0.25 and 0.5% acetic acid in drinking-water for periods of from nine to 15 weeks. Fluid intake was the same in all groups; at the 0.5% level there was immediate progressive reduction in body weight gain, loss of appetite and fall in food consumption to 27% of controls. The mortality rate was unaffected (Sollmann 1921, as cited in JECFA 1974). In another experiment, groups of three to four rats survived 14 days when given 1,800 mg/kg bw per day of the free acid intragastrically or 4,200-4,800 mg/kg bw of sodium acetate, but only three to five days on daily intragastric 2,400 mg/kg bw of the free acid. Animals lost weight before death and showed blistered paws and reddened noses. No autopsies were done (Hemmingway & Sparrow 1942, as cited in JECFA 1974). Intragastric intubation of 3 ml of a 10% solution of acetic acid (about 1,200 mg/kg bw/day) to rats for 90 days produced a drop in hemoglobin concentration and erythrocyte count (Wysokinska 1952, as cited in JECFA 1974).

Four groups of two young pigs fed daily diets containing 0, 240, 720, 960 or 1200 mg acetic acid/kg bw per day for successive 30-day periods to a total of 150 days showed no significant differences in growth rate, weight gain, early morning urinary ammonia, or terminal blood pH between controls and test groups. No autopsies were done (Lamb & Evvard 1919, as cited in JECFA 1974).

JECFA (1974) reported that about 1 g/day of acetic acid present in vinegar and other items of food and drink has been consumed by man for centuries apparently without causing any adverse effects. By comparison, the potential intake from its presence in maple fiber is trivial.

6.6.3.2 Formic Acid

Formic acid is the first member of the homologous series of fatty acids with general formula RCOOH. This acid was obtained first from the red ants; its common name is derived from the name for ants, *Formicidae*. This substance also occurs naturally in bees and wasps and is presumed to be responsible for the sting of these insects. Formic acid, in the form of its anion, formate, is naturally present in a large variety of plants; it is reported to be present in *Cistus labdanum* and the oil of *Artemisia transiliencies*. It is also found among the constituents of petit grain lemon and bitter orange essential oil, in strawberry aroma and in apple, sweet cherry, papaya, pear, raspberry, strawberry, peas, cheeses, breads, yogurt, milk, cream, buttermilk, raw fish, cognac, rum, whiskey, cider, white wine, tea, coffee and roasted chicory root. Formic acid is approved as a synthetic flavoring substance and adjuvant, acceptable "when used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice" (21 CFR 172.515).

JECFA (2003) identified no safety concern for formic acid when used at current levels of intake as a flavoring agent, and identified an ADI of 3 mg/kg bw/day.

Hanzlik et al. (2005) reported that ingestion of a single dose of 3,900 mg calcium formate (equivalent to 1.38 g formic acid) produced a transient increase in blood formate level, but no adverse effects in healthy humans, and Altaweel et al. (2009) reported that the same total dose of calcium formate given as 1,300 mg three times a day for 14 days produced no accumulation of formate and no signs of toxicity in healthy humans. Mean peak serum formate levels in these studies were in the range of 0.5 to 0.6 mM (23-28 mg/L). Because of the buffering capacity of body tissues and the equilibration between formate ion and formic acid, the effects of ingestion of formic acid or its salts would be expected to be equivalent, unless the concentration of formic acid was high enough to cause local effects due to low pH.

Metabolism to formate is responsible for the main toxic effects of ingested methanol (Altaweel et al. 2009; Liesivuori & Savolainen 1991; Sokoro et al. 2007; Zakharov et al. 2015), but sustained serum formate levels above 7 mM (320 mg/L) are needed to produce toxicity in rats or humans (Eels et al. 1996; Altaweel et al. 2009). Zakharov et al. (2015) reported on a series of 38 methanol poisoning cases. Among these cases, asymptomatic patients had median serum formate levels of 1.9 mM (87 mg/L; intraquartile range (IQR) 1.5-2.4 mM), while the median serum formate was 15.2mM (700 mg/L; IQR 13.9–17.6 mM) in symptomatic subjects with visual disturbances, 15.4 (IQR 12.1–18.0) mM in subjects with dyspnoea and 15.7 (IQR 12.8–18.5) mM in comatose patients. Similarly, Hovda et al. (2005) reported serum formate concentrations of 0.5 – 8.3 mM (23 – 380 mg/L) in four asymptomatic subjects who had consumed methanol, while symptoms of poisoning (increased anion gap, increased osmolal gap, and metabolic acidosis) were seen in 11 other patients with higher serum formate concentrations (up to 32 mM; 1470 mg/L), three of whom died.

In research conducted by Malorny (1969), it was stated that formic acid and its salts are not harmful to health up to certain limits due to the endogenous nature of formic acid and that it can completely degrade and be excreted with no risk of accumulation. In this context, it is notable that in its approach to the safety assessment of flavoring agents, JECFA (2000a) notes that:

> "*Endogenous substances* are intermediary metabolites normally present in human tissues and fluids, whether free or conjugated; hormones and other substances with biochemical or physiological regulatory functions are not included. The estimated intake of a flavouring agent that is, or is metabolized to, an endogenous substance should not give rise to perturbations outside the physiological range."

On this basis the low level of formic acid that may be present in maple fiber would not present a health risk, particularly since the upper usage intake rate is about one-thirtieth of the JECFA (2003) ADI.

6.6.3.3 Glyceraldehyde

Glyceraldehyde is a normal intermediate metabolite in glycolysis in mammals, and is a product of the Maillard reaction that occurs during cooking of food (Van Boekel 2006; Martins et al. 2001). As a result, it is present at low levels in the diet. Furthermore, because it is a normal human intermediary metabolite, it is found naturally in blood (Jonas et al 1989). These authors reported serum glyceraldehyde levels of 133 ± 59 µg/mL in normal subjects. Since normal human blood volume is 70 mL/kg bw (Lemmens et al. 2006), and serum constitutes about 54% of total blood volume, the human body normal contains about 5 mg/kg bw of glyceraldehyde. By comparison, the intake of 0.004 or 0.008 mg/kg bw of glyceraldehyde from maple fiber is trivial, and presents no health risk

6.6.3.4 Glycolic Acid

Like other acids, high concentrations of glycolic acid can be skin and eye irritants, but this would not be expected at the very low concentrations potentially present in maple fiber. Because glycolic acid is metabolized to oxalic acid, a known kidney toxicant, high doses of ingested glycolic acid can cause

kidney damage (Andersen 1998). Such effects were reported in rats fed diets containing 1% glycolic acid or more, but no adverse effects were seen when the dietary concentration was reduced to 0.5% (approximately 250 mg/kg/day) (Andersen 1998). This NOAEL is more than 5,000-times greater than the maximum dose of glycolic acid someone ingesting maple fiber might ingest (Table 12). This very low amount of glycolic acid presents no health risk to consumers.

6.6.3.5 Levulinic Acid

Levulinic acid has been assessed by FEMA (1984) and JECFA (2000b) identified it as being safe for flavoring use. It is also approved as a flavoring substance by FDA in 21 CFR 172.515. In the FEMA (1984) evaluation, it was reported that no toxic effects, no effect on growth rate, and no pathologic changes in internal organs were observed in rats fed diets containing 2% levulinic acid (about 1,000 mg/kg bw/day; approximately 167 mg/kg/day when scaled allometrically to an equivalent human dose) for 16 days. Also, no adverse effects were seen in men receiving levulinic acid at 43 mg/kg bw/day or 80 mg/kg bw/day in fruit juice for 30 days. It is considered relatively nontoxic with an oral LD50 in rats of 4g/kg (FEMA 1984).

The very low level of levulinic acid that might be present in maple fiber, thousands of times lower than the level producing no adverse effects in rats or humans, presents no health risk to consumers.

6.7 Conclusions

Based on a review of all of the available data pertinent to the safety of oral exposure to lignin and cellulose of small particle size, and the available information on the composition, particle size, and anticipated exposure level of Renmatix's maple fiber material, we conclude that maple fiber is safe and GRAS. The proposed uses of maple fiber will provide intakes of cellulose and lignin that are no greater than those produced by other GRAS sources of these substances, and will not result in intakes of cellulose hydrolysis breakdown products, or other byproducts, that could be harmful. The proposed uses and usage levels are, therefore, GRAS

We have reviewed the available data and information related to the components of Renmatix's maple fiber material and are not aware of any data and information that are, or may appear to be, inconsistent with the conclusion of its GRAS status.

Part 7. List of Supporting Data and Information

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