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Larex, Inc.

Arabinogalactan

GRAS Notification Document

October 15, 1998

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October 15, 1998

Dr. Laura Tarantino
Acting Director
Office of Premarket Approval
Center for Food, Safety and Nutrition HFS 200
Food and Drug Administration
200 C St. SW
Washington, DC 20204

Dear Dr. Tarantino:

In accordance with the proposed rule for Substances Generally Recognized as Safe, which was published in the *Federal Register* at Vol. 62, No. 74 on April 17, 1997, Larex, Incorporated (Larex) of St. Paul, Minnesota would like to submit a notice of a claim for exemption for the general use in foods of arabinogalactan (AG). Arabinogalactan is a natural polysaccharide which can be commercially extracted from trees of the genus *Larix* (larch), using water as the only solvent. Analytically, arabinogalactan is a soluble dietary fiber (80-85%) according to AOAC methods.

Larex is aware that a previous food additive petition for arabinogalactan was submitted jointly by Stein Hall and Company and St. Regis Paper Company in 1964. This petition was subsequently approved on February 25, 1965 as §121,1174. The regulation for arabinogalactan as a food additive was subsequently codified at 21CFR §172.230 and §172.610. The regulation approved the use of AG as an emulsifier, stabilizer, binding or viscosity agent for essential oils, flavors, non-nutritive sweeteners, salad dressings and pudding mixes.

The original petitioners envisioned arabinogalactan as a substitute for imported gum arabic, and did not envision that it might have broader uses. Two factors now allow for AG to be considered for more general use in the food industry. In the intervening decades since the original food additives petition was filed, researchers, both academic and within the food industry have identified and published expanded applications for arabinogalactan. Additionally, Larex has developed an improved process for arabinogalactan extraction, which produces products that are more acceptable to the food

industry. These new products are more highly purified than their earlier counterparts. Early versions of AG were hindered from entrance into the food industry by their dark color and astringent flavor. Heightened interest in soluble fibers by the food industry makes a safety assessment for expanded uses of arabinogalactan appropriate at this time.

A GRAS Report in support of the safe use of arabinogalactan in foods was prepared by Larex, and was reviewed on January 16, 1998 by a panel of experts qualified by training and experience. Those experts concurred with Larex's determination that arabinogalactan is safe for general use in foods.

On March 19, 1998 Larex personnel presented the salient points of the GRAS Report, and the conclusions of the expert panel to officials in the Center for Food Safety, and Applied Nutrition (CFSAN). At that time, Larex officials were invited by CFSAN personnel to consider submitting a notice of a claim for premarket exemption based on a GRAS determination under proposed §170.36.

Consequently, Larex has prepared a notification document in triplicate, which accompanies this letter. Larex would appreciate notice of the receipt of this document, and looks forward to any comments the agency would care to make on the notification.

Thank you very much for your attention to this matter. If you have any questions regarding the content of the notification, you may reach me at the number listed above.

Sincerely,

Lee B. Dexter
Technical Consultant

CC: Mr. Michael Finney, Larex
Mr. Robert Nickoloff, Larex
Mr. Richard Lamb, Larex
Dr. Arthur Lippman, CFSAN
Dr. Linda Kahl, CFSAN

Table of Contents

Item	Tab/Page
Letter	Letter
Table of Contents	Table of Contents
Notification Document	Notification Document
Introduction	1
References	References
Section I: Chemical Identity of Arabinogalactan	3
A. Common or Usual Name and Identity	3
B. Formal Names (IUPAC or Chemical Abstracts Names)	3
C. Synonyms, Other Common Names, Tradenames	3
D. Chemical Formulae, Structures and Molecular Weights	4
E. Chemical Abstracts Service Registry Number (CAS Registry No.)	4
F. Specifications for Food Grade Materials	4
G. Quantitative Composition of Arabinogalactan	4

Table of Contents
Section I (continued)

Item	Page
H. Manufacturing Process	6
I/J. LAREX Product Identification	8
Table 1 Larex Arabinogalactan Products	9
Table 2 Larex Product Specific Processing Steps	10
K. Molecular Weight Determination by Light Scattering	10
M. Analytical Methods	10
N. Raw Data - Arabinogalactan LSC-1 Western Larch	10
O. Raw Data - Decolorized Arabinogalactan - Western Larch	10
P. Raw Data - Arabinogalactan LSC-1 from Tamarack	10
Q. Natural Sources of Arabinogalactan	11

Table of Contents

	Tab/Page
Section II: Use and Functionality	12
A. Introduction	12
B. History of Use	12
Table 1: Composition of the Fractionated Pentosan-Protein Complexes of Wheat	15
C. Current Use	18
D. Exposure	18
E. Nutritional Analysis of LAREX Decolorized Arabinogalactan	19
F. Experimental Applications With Arabinogalactan in Baked Goods and Tableting	20
G. Functionality	23
Table 2 Functional Aspects of Arabinogalactan	26
Section III: Analytical Method for Arabinogalactan	28

Table of Contents

	Tab/Page
Section IV: Arabinogalactan: Its Safety when Consumed as an Ingredient in Processed Food	29
A. Introduction and Description	29
B. Arabinogalactan from Western Larch	30
C. Stein, Hall and Company & St. Regis Paper Company Food Additive Petition	31
D. Arabinogalactan Feeding and Safety Studies	32
E. Arabinogalactan Fermentation by Human Fecal Bacteria	35
F. Assay for Mutagenicity	35
G. Neutral Red Uptake Bioassay	40
H. Arabinogalactan and Insulin Response	40
I. Current Safe Use of Arabinogalactan	41
Section V: Environmental Assessment	41

LAREX, Inc. Arabinogalactan GRAS Notification

Introduction to the Notification Document

LAREX, Inc. (LAREX) has developed a twelve-volume GRAS report in support of a determination that its arabinogalactan products can be considered generally recognized as safe when used as food ingredients in accordance with current Good Manufacturing Practices. This report was reviewed by a panel of experts qualified by training and experience on January 16, 1998. The panel concurred with Larex, Inc., that its arabinogalactan products could be considered generally recognized as safe. The panel's findings and the salient points of the report were presented to various representatives of the Center for Food Safety and Applied Nutrition of the United States Food and Drug Administration on March 19, 1998. This notification document summarizes the twelve-volume report. References listed in this document can be found in the report, which has been placed in a Master File with the agency.

The arabinogalactan is extracted from trees of the genus *Larix* using water as the only solvent [Whistler, et al., 1970, VOL. 5 TAB 10 and Whistler, et al., 1991, VOL. 5 TAB 9]. LAREX is aware that a previous food additive petition was submitted, and subsequently approved by the Food and Drug Administration (FDA) in the early 1960's [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 5]. However, the petitioners, Stein, Hall and Company and St. Regis Paper Company were, at the time, focused on positioning the extracted arabinogalactan, then called Larch gum, as a substitute for expensive imported gums such as gum arabic. Hence, the original petitioners did not envision that arabinogalactan could be utilized in a wide variety of food products at expanded use levels [CRC, 1972, VOL. 10 TAB 7 and Anderson, 1966, VOL. 3 TAB 2]. Therefore, LAREX has prepared this report in support of a general recognition of safety for arabinogalactan in a wider market, which is poised to value not only the soluble fiber content of arabinogalactan but its unique functionalities as well.

The arabinogalactan derived from trees of the genus *Larix* (Larch) is a unique hemicellulosic product, in that it is easily extractable by water in a pure form from non-delignified plant tissues. Other hemicellulosic products have required chemical additives and/or mechanical treatments to extract them from their plant sources, and the literature has indicated that these extractants alter the polysaccharides to a certain degree [Whistler, et al., 1970, VOL. 5 TAB 9, Stephen, 1983, VOL. 4 TAB 8, and Wilkie, 1986, VOL. 5 TAB 12]. Therefore, the arabinogalactan produced by LAREX can

be considered equivalent to naturally occurring arabinogalactan [Whistler, et al., 1970, VOL. 5 TAB 9].

Many authors have demonstrated that arabinogalactan is a common constituent of plant cell walls, and as such has had a long history of consumption by humans [Pennell, et al., 1989, VOL. 4 TAB 1]. Arabinogalactans are often complexed with protein to form a glycoprotein which has various functions in the plant cell wall [Stephen, 1983, VOL. 3 TAB 22, and Schindler, et al., VOL. 4 TAB 6]. Arabinogalactans have been commonly consumed by humans in such foods as maple syrup, carrots, tomatoes, soy beans, radishes, and wheat flour [Neukom, et al., 1975, VOL. 3 TAB 24, Morita, et al., 1965, VOL. 5 TAB 9, and Whistler, et al., VOL. 5 TAB 9]. Arabinogalactan has a number of valuable properties for use in foods including moisture retention, emulsification, thickening, bulking, and the nutritional benefits of its soluble fiber content [Table 5, VOL. 6 TAB 12]. The addition of extracted arabinogalactan to various foods, including baked goods such as cakes, cookies and yeast raised breads, has demonstrated a self-limiting level, beyond which the quality of the product begins to decline [American Institute of Baking, 1997, VOL. 6 TAB 5].

The LAREX products are produced in a food grade plant in Cohasset, Minnesota, which complies with all state and federal regulations regarding food production. Therefore, LAREX believes that its arabinogalactan product can be considered generally recognized as safe when consumed as a food ingredient, and submits the following report to support that position.

Section I: Chemical Identity of Arabinogalactan

A. Common or Usual Name and Identity

Arabinogalactan is a polysaccharide composed of galactose and arabinose units with a highly substituted back bone of β 1-3 linked galactopyranose units and side chains of galactose and arabinose [Whistler, et al., 1991, VOL. 5 TAB 9].

1. Arabinogalactan
2. Galactoarabinan
3. Arabogalactan
4. Larch Gum
5. Larch wood sugar

B. Formal Names (IUPAC or Chemical Abstracts Names)

1. Galactorabinan
2. L-arabino-D-galactan

C. Synonyms, Other Common Names, Tradenames

1. Stractan 2
2. Stractan 10
3. Stractan 15
4. Larch wood sugar
5. LSC-1
6. L'Extra F500
7. L'Extra F100
8. FIBERAID

9. L'Extra F2000

D. Chemical Formulae, Structures and Molecular Weights

1. The chemical structure of arabinogalactan can be described as $[(C_5H_8O_4)(C_6H_{10}O_5)_6]_x$.

2. Molecular Weight: 16,000 - 25,000

E. Chemical Abstracts Service Registry Number (CAS Registry No.)

1. CAS number 9036-66-2

F. Specifications for Food Grade Raw Materials

LAREX has developed a set a food grade specifications for the raw materials used in its manufacturing process, including Larch logs, food grade hydrogen peroxide, and potassium hydroxide [VOL. 2 TAB 2]. It has also developed a set of final product specifications for its arabinogalactan products, which can be utilized to describe the product [Table 1, VOL. 2 TAB 3]. These specifications include a determination of the arabinogalactan percent by refractive index, specific gravity, color, phenol content, turbidity, chloride content, viscosity, molecular weight, and insoluble matter [Table 1, VOL. 2 TAB 3].

G. Quantitative Composition of Arabinogalactan

Arabinogalactans from Larch species have a backbone of (1-3)-linked β-D-galactopyranosyl units, each of which bears a substituent at the C-6 position. Most of these side chains are galactobiosyl units containing a (1-6)-β-D-linkage. Another common side chain consists of single L-arabinofuranosyl or of 3-O(β-L-arabinopyranosyl)-α-L-arabinofuranosyl units. Small amounts of D-glucuronopyranosyl units are present in arabinogalactans from European Larch and in Tamarack. In most species of arabinogalactan the ratio of L-arabinosyl units to D-galactosyl units is 1:6 [Whistler, et al., 1970, VOL. 5 TAB 10 and Whistler et al., 1991, VOL. 5 TAB 9]. Larch arabinogalactans have been reported to contain two fractions with molecular weights of 16, 000 and 100,000 [Borgin, et al., 1949 VOL. 3 TAB 1, and Bouveng, et al., VOL. 3 TAB 7]. Other investigators found two components with molecular weights of 18,000 and 78,000. Using Smith degradation, both fractions yielded a product of 2,200 Da indicating blocks of about 12 β-D-galactopyranosyl units separated at regular intervals by sugar units vulnerable to periodate

oxidation [Churms, et al., 1978 VOL. 3, TAB 8]. More recent studies have indicated that there is aggregating behavior in arabinogalactans, and the arabinogalactans produced by LAREX routinely obtain number average molecular weights between 15,000 and 25,000 [Table 1, VOL. 2 TAB 5].

Arabinogalactans are often linked covalently to protein. When short chains of the two sugars are joined glycosidically to hydroxyl groups in peptide chains, they are termed glycoproteins [Stephen, 1983, VOL. 4 TAB 8]. The term glycoprotein also embraces carbohydrate moieties with monosaccharide and derived monosaccharide components much wider in scope than the arabinose and galactose units under consideration. These arabinogalactan -proteins are thought to function in plant cell communication and defense [D'Adamo, 1990, VOL. 10 TAB 9].

Arabinogalactans from Larch wood have been studied since the beginning of the century, and their chemistry has been the subject of many reviews [Whistler, et al., 1991, VOL. 5 TAB 9, Wilkie, 1986, VOL. 5 TAB 12, and Timell, 1965 VOL. 4 TAB 11]. The Larch wood arabinogalactans are a Type II arabinogalactan, the arabino-3, 6-galactans type which is the most prevalent class of arabinogalactan. It is also found in the exudate gums of gymnosperms, such as trees of the genus *Larix,* and in angiosperms such as the *Acacia* tree. The other types of arabinogalactans are Type I, the arabino-4-galactans, and the Type III, which are polysaccharides containing arabinogalactan side chains [Stephen, 1983, VOL. 4 TAB 8].

As early as 1942, the molecular weight of arabinogalactan from Larch wood was determined, and two fractions were identified: high-molecular weight fraction of 100,000 Da, and a lower-molecular weight fraction of 16,000 Da [Borgin, 1949, VOL. 3 TAB 25]. The variability of arabinogalactan content in different parts of the tree or the effects of seasonal variations as well as other factors make the significance of this molecular weight disparity unclear. Values of optical rotation that have been reported for arabinogalactan from gymnosperms are usually low and positive [Timell, 1965, VOL. 4 TAB 11]. The general conclusion from many structural studies involving species of *Larix* such as *occidentalis, desidua, laricina, lyallii, leptolplepis, and korean* is that there is considerable similarity among the constituent groups of sugar residues attached to the (1-3)-linked D-galactan chains [Stephen, 1983, VOL. 4 TAB 8, Odonmazig, 1994, VOL. 3 TAB 25, and Whistler, et al., 1970, v 5 TAB 10].

The ratio of galactose to arabinose is consistently 6:1 among the samples of arabinogalactan from Western Larch. Arabinogalactan concentrations in *Larix occidentalis* are highest at the lower end of the tree in the butt wood where concentrations have been reported to reach from 5-25%

[CRC, 1972, VOL. 10 TAB 7, and BeMiller, 1989, VOL. 3 TAB 5]. High concentrations of arabinogalactan can also be extracted from the Tamarack, (*Larix laricina)*, however, distribution of the arabinogalactan is significantly different in that species, reaching highest concentrations distally from the center of the tree [Cote`, et al., 1967, VOL. 3 TAB 9].

Analysis of five lots of the LSC-1 arabinogalactan product from Western Larch (*Larix occidentalis)*, and the LSC-1 product from Tamarack (*Larix laricina*), revealed that arabinogalactan from both species tested met the specifications set out for a food grade product by LAREX [Tables 1, 3 and 4, VOL. 2 TABS 3, 5, and 7]. Both products contained less than 3 ppm arsenic, less than 5% ash, and less than 10 ppm heavy metals as lead. They each contained 50-55% arabinogalactan in solution with a pH of 3.0 to 6.0, specific gravity in a range from 1.18 to 1.75, and negligible insoluble matter (less than 0.1%). Phenol content ranged between 1.0 and 3.0 ppm. The turbidity of the solutions as measured in Nephelometric Turbidity Units (NTUs) was between 0.5 and 5.0. Molecular weights as determined by HPLC/GC were 16,000 to 25,000 and UV reflectance at 280 nm was between 0.55 and 1.20. Chloride content was less than 150 ppm, and viscosity was less than 500 cps.

Microbial content of both products was remarkably low, easily meeting the specifications set forth by LAREX of less than 1,000 CFU for aerobic plate counts, negative for *Salmonella*, mold counts of less than 100, yeast counts of less than 100, and *Staphylococci* less than 10. Actual values were negative for *Salmonella*, and 10 or <10 for all other microbial parameters [Table 5, VOL. 2 TAB 8].

Heavy metal content of the products showed that all USP heavy metals were below the level of detection, (5.0 ppm). Mercury was also below the level of detection (0.01 ppm), arsenic ranged from <0.01 ppm to 1.7 ppm, and chromium ranged from 0.06 ppm to <0.06 ppm [Table 11, VOL. 2 TAB 14]. Benzene and organo-phosphorus pesticide results were below the level of detection for all products [Table 9, VOL. 2 TAB 12]. These data indicated that there was no species difference in the quantitation of the arabinogalactan product, and both species met the food grade specifications set forth by LAREX.

H. Manufacturing Process

The extraction of Larch arabinogalactan is unique among hemicellulosic extraction processes. Other hemicellulosic extraction procedures require harsh chemicals to release the polysaccharide from the plant matrix [Whistler, et al., 1970, VOL. 5 TAB 10, Wilkie, 1986, VOL. 5 TAB 11, and Wolf, et al., 1953, VOL. 5 TAB 13]. These chemicals used for other

extraction processes are known to change the structure and the stereochemistry of the extracted polysaccharide [Whistler, et al., 1970, VOL. 5 TAB 10, Wilkie, 1986, VOL. 5 TAB 11, and Stephen, 1983 VOL. 4 TAB 8]. Larch arabinogalactan is present in sufficient quantities that it can be extracted with water. The resulting product is a pure and structurally unaltered form of hemicellulose in its natural state [Whistler, et al., 1970, VOL. 5 TAB 10, Whistler, et al., 1991, VOL. 5 TAB 9, and Wilkie, 1986, VOL. 5 TAB 12].

LAREX manufactures arabinogalactan at its plant in Cohasset, Minnesota. All processing is conducted under current Good Manufacturing Practices. All raw materials comply with food grade specifications or the specifications set forth by LAREX for natural materials. HACCP and sanitation programs are in place to assure that the process produces a product consistent with the final product specifications [VOL. 2 TAB 18]. A written recall program has also been established to ensure that product can be tracked by lot number in the event of a general recall [VOL. 2 TAB 19].

In the processing scheme, the butt cuts of large larch logs are brought to the plant via rail and truck. These log sections are first put through a debarker, and debarked logs are then split and chipped. The resulting wood chips are conveyed to a silo where they are stored until the chips are moved to a steam bin for heating. Steamed chips are fed via a plug screw feeder, extracted, and fed through a hot water impregnator. A second plug screw feeder further extracts the arabinogalactan which is then screened to remove any cellulosic particles. Screened pressate is then sent to an extract storage tank where purified water is added. The extract is then further heated with steam before being sent through a pall separator. The permeate from this separation contains 7% arabinogalactan by weight. This dilute solution is then sent to an evaporator, which utilizes steam for heat. Condensate from the evaporator is recycled after being solubilized with 50% sodium hydroxide.

The product of the evaporator contains 50-55% arabinogalactan, and is ready for drumming and shipping as either a food material or an industrial processing aid. Typically, a small quantity of potassium sorbate is added to the product at this time as a preservative [Wilkie, 1986, VOL. 5 TAB 12]. Optionally, this liquid product can be sent through an ion exchange step to further purify the liquid before it is spray dried, or it can be decolorized, and further processed to reduce color, odor, and flavor. The decolorization is accomplished by treating the product with specified quantities of 45% potassium hydroxide and 35% hydrogen peroxide solutions. After decolorization, the product is then cooled via cooling water. Following cooling, the concentration of the bulk arabinogalactan in

solution is 35%. This product may enter one of several streams following decolorization and cooling: 1) it may be directly spray agglomerated; 2) it may be sent through a carbon filter followed by spray agglomeration; 3) it may be sent through a carbon filter and an ion exchange step prior to being spray agglomerated; or 4) it may go directly through an ion exchange step, a spray drying step and then be agglomerated.

Historical Extraction Processes

Attempts at extraction of arabinogalactan from Western Larch (*Larix occidentalis)* have a long history dating back to the years 1914-1922. Various historical extraction procedures are reviewed in the petition [Adams, 1960, VOL. 3 TAB 1, Jensen, 1960, VOL. 3 TAB 18, U.S. Patent No. 160,777, 1922, VOL. 4 TAB 12, U.S. Patent No. 1,816,135, 1931, VOL. 5 TAB 1, U.S. Patent No. 2,073,616, 1937, VOL. 5 TAB 2, U.S. Patent No. 2,801,955, VOL. 5, TAB 3, U.S. Patent No. 3,325,473, 1967, VOL. 5 TAB 4, and U.S. Patent No. 3,337,526, 1967, VOL. 5 TAB 5]. The extraction procedure used by Stein, Hall and Company and St. Regis paper Company was based on counter current leaching, and was described in their food additive petition [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15]. This process consisted of extracting the Larch wood at temperatures ranging from ambient to 150°F. After a total of 20 hours of extraction time the concentrated liquor was dried on a steam-heated drum to yield what was described as a light tan powder. The extract liquor was reported to contain up to 20-25% arabinogalactan. However, the company found it expedient to stop the extraction at a concentration of approximately 12%. Several improvements were made on this basic process including the introduction of screw presses and magnesium oxide to precipitate impurities. These improvements were subsequently patented [U.S. Patent No. 3,325,473, 1967, VOL. 5 TAB 4, U.S. Patent No. 3, 337 526, 1967, VOL. 5 TAB 5, and U.S. Patent No. 5,116,969, 1997, VOL. 5 TAB 7]. Building on this historical experience, LAREX has developed the process described above which has been credited with producing a product more desirable to the food industry both from an economic and a quality standpoint.

I/J. LAREX Product Identification

The LAREX arabinogalactan products are of several types. The initial extractant from the process is purified through a pall separator, and is then evaporated to a 50% arabinogalactan concentration. This product is called LSC-1. At this point the product may either enter the printing industry as LaraPrint 100 or to the food industry as L'Extra F100, or it may be further purified though ion exchange to improve color, taste, and odor. Additionally, the product may be decolorized utilizing hydrogen peroxide

and potassium hydroxide. Finally, the products may be spray dried and agglomerated. A listing of the various arabinogalactan products manufactured by LAREX and their respective processing steps is given in the two tables below.

Table 1
LAREX Arabinogalactan Products

Arabinogalactan Product Name	Market and Properties of Products	Market
LaraPrint ™ B50	Ink additive for decreasing viscosity while maintaining color density: caramel colored 50% solution preserved with potassium sorbate.	Printing and inks
LaraPrint ™ B100	Ink additive for decreasing viscosity while maintaining color density: tan colored powder	Printing and inks
L'Extra F100	A fiber source: off-white powder, very low taste and odor, no precipitation in liquids, excellent dissolution.	Food and Beverage
LaraCare™ A200	Emulsion stabilizer, film and gloss former, dispersant, moisture control, rheology control: off-white powder, mild odor, highly soluble, excellent dissolution, and biodegradable.	Personal Care
L'Extra™ F2000	Moisture control: mouthfeel, encapsulation, bulking agent: off-white powder, low viscosity, very low taste and odor, some precipitation in liquids, excellent dissolution, used for moisture control.	Food and Beverage
FIBERAID™	A fiber source: off-white powder, very low taste and odor, no precipitation in liquids, excellent dissolution.	Food and Beverage

Table 2
LAREX Product Specific Processing Steps

Arabinogalactan Product Name	Processing Steps
LaraPrint ™ B50	extraction, screening, separation, evaporation, preservative addition
LaraPrint ™ B100	extraction, screening, separation, evaporation, preservative addition, spray drying
L'Extra F100	extraction, screening, separation, evaporation, preservative addition, spray drying
LaraCare™ A200	extraction, screening, separation, evaporation, decolorizing, ion exchange, spray drying, agglomeration
L'Extra™ F2000	extraction, screening, separation, evaporation, decolorizing, carbon filtering, spray agglomeration
FIBERAID™	extraction, separation, evaporation, decolorizing, carbon filtering, ion exchange, spray agglomeration

K. Molecular Weight Determination by Light Scattering

In March of 1997, LAREX contracted with Scientific Polymer Products, Inc. to determine the molecular weight of its arabinogalactan product Lot No. 97A009-2 by light scattering. Results showed that molecular weight via light scattering ranged between 57,300 and 73,600 Da. Molecular weight by number ranged from 51,900 to 63,600.

M. Analytical Methods

LAREX has provided written analytical methods and procedures for the determination of its specification parameters. These methods include a description of the equipment to be used, the concentrations of any solutions to be used, and a set of sample calculations.

N. O. P. Raw Data

Sections N., O., and P. contain the raw data from the various arabinogalactan product analyses.

Q. Natural Sources of Arabinogalactan

Arabinogalactans have been documented from many sources. A number of review articles indicate that arabinogalactan and arabinogalactan proteins are present in the plant cell walls of nearly all higher land plants. They have been documented in mosses, wheat flour, soy beans, *Pinus cortata*, carrots, grapes, and radishes [Geddes, et al., 1971, VOL. 3 TAB 13, Laidlaw, et al., 1962, VOL. 3 TAB 20, Morita, 1965, VOL. 3 TAB 22, Pennell, et al., 1989, VOL. 4 TAB 1, Saulnier, 1992, VOL. 4 TAB 4, and Neukom, et al., 1975, VOL. 2 TAB 24]. These references indicate that arabinogalactans are wide spread in the plant kingdom and thus have been historically been utilized by man as a food source.

Section II: Use and Functionality

A. Introduction To Functionality

Arabinogalactan and arabinogalactan proteins are common components of plant cell walls, and in their natural state enter the human food chain in such common food substances as wheat flour, radishes, tomatoes [Pogson, et al., 1995, VOL. 7 TAB 13]. Due to its highly branched structure, arabinogalactan is highly soluble in water, and relatively high concentrations of arabinogalactan are very low in viscosity [D'Adamo, 1990, VOL. 6 TAB 10]. This unique set of characteristics has led arabinogalactans to be considered as an ingredient in a wide array of food materials. Much of the evidence for the applicability of arabinogalactan comes from the patent literature, where applications involving arabinogalactan have ranged from edible films to a component of artificial sweetening systems [U.S. Patent No. 3,294,544, VOL. 7 TAB 19, U.S. Patent No. 4,288,198, VOL. 7 TAB 23, and U.S. Patent No. 5,089,307, VOL. 8 TAB 8].

Recent baking studies with arabinogalactan in breads, cakes, tortillas, and cookies have shown that the addition of arabinogalactan contributes positive characteristics to baked goods (fineness of grain), and the product appears to have a self-limiting level which, when exceeded produces a product whose total quality is less than comparable controls [American Baking Institute, 1997, VOL. 6 TAB 5]. Experiments with arabinogalactan as a tableting aid have shown that a 5% addition will increase hardness and improve dissolution [Fuji, 1990, VOL. 6, TAB 22]. These studies have demonstrated that arabinogalactan has a variety of functional attributes that would be desirable in the food industry.

B. History of Use

Arabinogalactans in Wheat Flour

Fincher, et al., 1974, reported that arabinogalactans have been isolated from plant tissues of diverse origin, and that they can be readily extracted, generally with water, from coniferous woods, coffee beans, soy bean seeds, aquatic moss, saguaro cactus cortex, apple fruit, rape seed, siratro leaves, broad-bean leaves, and from suspension-cultured cells of tomato and sycamore. In this study an arabinogalactan-peptide from wheat endosperm was studied using physiochemical techniques. Certain aspects of the chemical structure of this molecule were also published [Fincher, et al., 1974, VOL. 6 TAB 20].

The arabinogalactan-peptide was found to be a non-associating polydisperse macromolecule with a molecular weight of approximately 22,000. This molecule exhibited only minor non-ideal effects in aqueous solutions.

According to a review written by D'Appolonia, 1980, the primary non-starchy polysaccharides of wheat flour are the pentosans, which are classified as hemicelluloses. Some researchers have used the term hemicellulose to refer to the water-insoluble non-starchy polysaccharides and the word "pentosan" to the water-soluble polysaccharides. As an introduction, Medcalf and D'Appolonia, 1968, stated that wheat flour pentosans could generally be classified according to two types. The water-soluble pentosans and the pentosan associated with the water-insoluble or "sludge" portion of wheat flour. Both the water-soluble pentosans and those associated with the "sludge" fraction appear to be mixtures of free arabinoxylans and polysaccharide-protein complexes. Wheat flour pentosans appeared to play a role in the quality characteristics of both common bread wheat and durum wheat [Medcalf, et al., 1968, VOL. 7 TAB 7]. Arabinoxylans were also described in wheat by Neukom, et al., in 1967 [Neukom et al., 1967, VOL. 7 TAB 10].

One of the important properties of the water-soluble pentosans is their highly viscous nature when dissolved in water. It is in this respect that they contribute significantly to dough consistency. When a dough is formed water is taken up by the flour constituents in proportion to their solubility or hydration capacity. It has been reported that about 46% of the water in a dough is associated with the starch, 31% with the gluten, and 23% with the pentosans. The intrinsic viscosity of the polysaccharides in a water extract flour is 15-20 times larger than that of the soluble proteins extracted [D'Appolonia, 1980, VOL. 6 TAB 14].

Another important property of water-soluble pentosans is their ability to form a gel. It has been shown that a glycoprotein obtained by fractionation of pentosans with D-cellulose was responsible for the gelation reaction in the presence of an oxidizing agent. Loaf volume increased with the addition of water-solubles, and with the incorporation of crude and amylase treated pentosans. Addition of DEAE-cellulose pentosan fractions, which were essentially pure arabinoxylans, resulted in only a slight increase in loaf volume, and a detrimental effect on crust color. The high protein containing DEE-cellulose fractions had a definite effect in increasing loaf volume [D'Appolonia, 1980, VOL. 6 TAB 14].

A dramatic increase in bread loaf volume with the addition of a pentosan preparation was reported by workers who had isolated pentosan-containing material from whole rye kernels by means of an alkaline

containing material from whole rye kernels by means of an alkaline extraction. It was also found that more total water-solubles and crude pentosans were isolated from baked bread in a continuous system than from conventionally baked bread, although, there did not appear to be any major change in the composition of the pentosans of wheat flour when processed by either system [D'Appolonia, 1980, VOL. 6 TAB 14].

The pentosan composition of the average baker's patent flour was reported as 2-3%. Of this material, 0.8-1.5% was known to be soluble in cold water, the remainder, which had been called water-insoluble pentosans, was found associated with the tailing fraction. The two main sugar units found in the pentosan structure were D-xylose, and L-arabinose [D'Appolonia, 1971, VOL. 6 TAB 16].

Pentosans extracted from wheat flour exhibit an extremely hydrophilic nature. These pentosans are able to increase the water absorption of flour and workers utilizing a farinograph have demonstrated the effect of pentosans on water absorption. They reported that water-soluble pentosans, aribinoxylans, absorb 11 times their weight of water, and the water-insoluble pentosans, 10 times their weight. One author reported that pentosans, or pentosan-containing fractions, are responsible for a reduction in mixing time. The same author found that the addition of the complete water-soluble fractions extracted from flour to a gluten-starch baking system resulted in a pronounced increase in volume. Gilles has shown that the addition of pentosan in the making of a cake resulted in a product, which was superior to the control cake containing no added pentosans. Inclusion of the pentosans improved grain, texture and volume of the finished cake [D'Appolonia, et al., 1970, VOL. 6 TAB 15].

These fractions were found to be made up primarily of arabinoxylan and arabinogalactan, the later of which possessed a small protein residue [Meuser, et al., 1986, VOL. 7 TAB 8]. These authors also proposed a structure for soluble arabinoxylan and described a model structure for the arabinogalactan-peptide of wheat endosperm. According to this proposal, the basic chain of galactose was branched. The authors attributed the high degree of solubility of the arabinogalactan-peptide to the high degree of branching within the molecule.

Based on their investigations, the researchers listed the yield of arabinoxylan and arabinogalactan protein complexes from wheat.

Composition of the Fractionated Pentosan-Protein Complexes of Wheat
Table 1

Fraction	Yield (g/100g flour d.m.)	Protein content (% d.m.)	Carbo-hydrate content (% d.m.)	Carbohydrate Composition (%) Ara	Xyl	Gal
Arabinoxylan-protein complex	0.58	10.8	86.4	34.7	64.7	traces
Arabinogalactan-protein complex	0.14	5.2	91.2	41.0	traces	59.0

Arabinogalactan in Coffee

Arabinogalactan has been found to be a significant component of the green coffee bean, comprising approximately 8.5% of the total weight. Wolfrom, et al, 1965, isolated arabinogalactan from green coffee beans and characterized the product as having an optical rotation of $[\alpha]^{25}_{D}$ -27⊕. The authors noted that the green coffee bean has a high content (50-60%) of polysaccharide. The constituent sugars of which have been determined to be β-mannose, L-arabinose, D-galactose, and D-glucose. The L-arabinose and D-galactose components have been established to be in the form of an arabinogalactan, which is slightly water-soluble. The authors reported that the polysaccharide is difficult to extract completely from the very hard green coffee bean, probably because of the cellular structure of this particular plant structure. The coffee bean arabinogalactan appeared to be associated with the protein faction which was likewise water soluble, and both were associated with the characteristic coffee acids which were largely aromatic [Wolfrom, et al., 1965, VOL. 8 TAB 22].

A continuation in the study of polysaccharides from coffee was conducted by Wolfram, et al., in 1967. In this report the researchers reported on two polysaccharides isolated from instant coffee powder. These polysaccharides were a mannan and an arabinogalactan. The L-arabinose content of the arabinogalactan was much lower however, than that previously found for the arabinogalactan of the green coffee bean. The authors speculated that this was due to the degradation caused by the roasting of the bean [Wolfram, et al., 1967, VOL. 8 TAB 23].

In a third study on arabinogalactans in coffee, DeMaria, et al., 1994, investigated arabinogalactan as a potential furfural precursor in roasted coffee [DeMaria, et al., 1994, VOL. 6, TAB 17]. The authors reported that a fraction, C_1, which was very rich in polysaccharide, was isolated from

high-molecular weight, water-soluble material obtained from green coffee. Polysaccharides represented about 88% of the total fraction C_1. After roasting, furfural was identified in fraction C_1 by means of head space-GC/MS analysis. Roasting of this fraction was reported to effect the arabinogalactan, promoting a high loss of arabinose residues. After roasting the arabinose content was reduced by 42.3% and the galactose content by 4.4%. The authors suggested that furfural found in fraction C_1 originates mainly from arabinogalactan. The authors further indicated that this result agreed with data from Wolfram, et al., 1967 [Wolfram, et al., 1967, VOL. 8 TAB 23]. The degradation of the arabinose residues from the arabinogalactan was strong evidence that one role of arabinogalactan was as a flavor precursor in fractions of C_1.

Arabinogalactan in Maple Syrup

G. A. Adams, 1962, published a research study whose purpose was to investigate water-soluble polysaccharides from a typical hardwood, sugar maple. The author mentioned that little information was available at that time on this subject, principally because of the low yields that were obtained from those sources. In this study only those polysaccharides which were extractable from extractive-free wood, that is, only those polysaccharides which were water extractable from sapwood, heartwood, and inner bark were studied. The yield of water-soluble polysaccharides from the three types of wood was: 1) heartwood - 0.39%, 2) innerbark - 1.03%, and 3) sapwood - 0.53%. In general, the heartwood polysaccharide was found to be somewhat higher in arabinose and galactose content than in glucose and mannose. The author indicated that since the composition of various polysaccharides were complicated mixtures, detailed studies in this publication were limited to the polysaccharides isolated from sapwood. Five polysaccharides were subsequently identified: 1) neutral arabinogalactan, 2) acidic arabinogalactan, 3) neutral xylan, 4) acidic xylan, and 5) a glucomannan. An arabinogalactan was isolated from the purified water-soluble polysaccharide with a specific rotation of $[\alpha]_D^{25}$ + 16.8⊕ in water. These studies were the first studies to show the structure of water-soluble polysaccharides from hardwood [Adams, 1962, VOL. 1 TAB 1].

Arabinogalactan in Radish and Tomato

Kikuchi, et al, published a report in 1993 which discussed the use of rabbit anitsera which was raised to react with arabinogalactan-proteins isolated from seeds, roots, or leaves of radish (*Raphanus sativus L.*) as revealed by immunodiffusion analysis. Electron-microscope observation of immunogold-stained tissues demonstrated that arabinogalactan-proteins were localized in the middle lamella as well as at the plasma membrane of primary roots of radish. Agglutination of protoplasts prepared from cotyledons occurred with the antibodies, supporting the evidence for localization of arabinogalactan-proteins in the plasma membrane. A previous study published by the authors on arabinogalactan-proteins isolated from different organs developed after germination of radish seeds demonstrated organ-specific variation of arabinogalactan-proteins with respect to chemical composition and serological activity. Transient production of L-fucose-containing arabinogalactan-proteins was characteristically observed in the primary roots of radish, indicating a developmentally regulated expression of arabinogalactan proteins in the root. It was anticipated that antibodies directed against sufficiently long consecutive β-(1-6)-galactooligosaccharides would provide a specific probe for arabinogalactan-proteins. The antiserum developed in this study was purified and used for histochemical localization of arabinogalactan-proteins in plant tissues [Kikuchi, et al., 1993, VOL. 7 TAB 2]. In a similar study Pogson, et al., described an arabinogalactan-protein from tomato [Pogson, et al., 1965, VOL. 7 TAB 12].

Arabinogalactan in Black Gram

Arabinogalactan has also been identified in black gram (*Phaseolus mungo*), a traditional common grain legume, which is an essential ingredient in some of the most popular and typical Indian breakfast foods. This breakfast food possesses a characteristic soft, spongy texture and is made out of leavened mixtures of the legume and other cereals such as rice. A noteworthy feature of batters containing this legume, according to the author, is their high viscosity ascribed to the presence of a mucilaginous principal that is also held to be responsible for the gas-holding and dough-raising qualities of this batter. Other legumes were reported to lack this principal.

The arabinogalactan was extracted with aqueous 10% (w/v) trichloroacetic acid and precipitated with acetone. Re-precipitation and dialysis yielded a homogenous mixture with a high molecular weight of approximately 144,000 as determined by gel filtration through Bio-Gel T-200. Aqueous dispersions of this polysaccharide possessed high viscosity near pH 5.7,

which decreased with increases in temperature [Susheelamma, et al., 1978, VOL. 7 TAB 15].

Historical Products from Larch Wood

Products have been extracted from the Larch trees native to Montana from as early as 1914. An article, published in the Timberman from 1922 describes such a product which was used as a leavening agent [LaMotte, 1922, VOL. 7 TAB 6]. A product called cream of milk sugar or mucic acid was created by extracting galactose from the Montana Larch in its complex form, hydrolyzing the fluid and then oxidizing it to form an acid derivative which became known as mucic acid. The product was described as being pure white in color, crystalline, and containing no impurities such as iron, arsenic, lead, calcium, or the salts of these metals. The taste of the product was described as tart-fruity, similar to citric acid and cream of tartar. The product was reportedly stable and did not deteriorate on standing. According to the author, it had approximately twice the working strength of cream of tartar and when made into baking powder found its widest use in the commercial baking industry in the form of a baking acid for the manufacture of self-rising flour. Also according to the author, it found wide usage in soft drinks, jellies, jams, ice cream, candy, and medicines [LaMotte, 1922, VOL. 7 TAB 6].

C. Current Use

The product is under consideration for use by major food companies in beverages, cereals, snacks, and baked goods.

D. Exposure

Detailed exposure data are not yet available for the LAREX, Inc. arabinogalactan products. However, an average maximum use level for arabinogalactan was considered by the Flavor Extract Manufacturer's Association expert panel in 1972. That panel based its judgment that arabinogalactan could be considered generally recognized as safe on the basis of an 85% use in candy [Oser, et al., 1972, VOL. 7 TAB 11]. More recent data has suggested that arabinogalactan has a self-limiting level in foods [American Institute of Baking test results, 1997, VOL. 6 TAB 5]. In baked goods with the exception of fat-free tortillas, product acceptability began to decline when arabinogalactan reached the 5% level on a flour weight basis. In general, acceptable use levels were less than 2% on a total formula basis.

Arabinogalactan has had a safe history of use, since its approval as a food additive in 1965. There have been no known incidents of toxicity resulting from consumption of arabinogalactan since that time.

E. Nutritional Analysis of LAREX Decolorized Arabinogalactan

Five lots of Larex decolorized arabinogalactan manufactured over a period of time were analyzed for nutritional components and for caloric content. The results showed that moisture content of the arabinogalactan ranged from 3.10 to 6.20%, and protein content ranged from 0.35 to 0.55%. Fat as determined by acid hydrolysis ranged from 0.00 to 0.50%. Ash content varied from 0.19 to 7.66%. The carbohydrate percentage ranged from 85.34 to 96.01. Total dietary fiber content ranged from 77.80% to 80.24%. Calories in Kcal/100 g ranged from 346.31 to 387.59 [Ingman Laboratories Data, 1997, VOL. 6 TAB 9].

It should be noted that these caloric values are considerably different from those reported earlier by the University of Wisconsin Research Foundation, who found that arabinogalactan extracted from Western Larch contained about one third the calories of corn starch [Wisconsin Alumni Research Foundation Report, 1963, VOL. 6 TAB 6]. This discrepancy is potentially due to the fact that the caloric content of soluble fiber under the new NLEA regulations of 1990 is now calculated with the same caloric content as any other carbohydrate (4 calories per gram), whereas previously, soluble fiber content was deducted from the total calories contributed by carbohydrates.

Arabinogalactan was found to be relatively low in mineral content, except for Potassium levels which ranged from 0.033% to 3.93% [Ingman Laboratories Data, 1997, VOL. 6 TAB 9].

These five lots of LAREX decolorized arabinogalactan products manufactured over a period of time were analyzed for four common sugars included in a sugar profile [Ingman Laboratories, Analytical Data, 1997, VOL. 6 TAB 9]. All samples showed that glucose, sucrose, maltose, and fructose were absent or non-detectable.

Lot No. 0034-97065-01 of decolorized arabinogalactan product was analyzed for fatty acid content by Ingman Laboratories in Minneapolis, Minnesota [Ingman Laboratories, Analytical Data, 1997, VOL. 6 TAB 9]. Of the total fatty acids present, 48.4% were saturated fatty acids, 39.10% were monounsaturated fatty acids, and 12.5% were polyunsaturated fatty acids. The major fatty acid constituents were palmitic 25.4%, aleic 36.0%,

stearic 15.5%, and linoleic 12.5%. Total fat of all samples measured by Ingman Laboratories, via acid hydrolysis, was less than 0.5%.

F. Experimental Applications With Arabinogalactan In Baked Goods And Tableting

Functionality of Arabinogalactan in Baked Goods

When arabinogalactan was added to various baked products a self-limiting level of addition was found in cookies and in straight dough white pan breads. Specific volume and total quality scores decreased with the addition of arabinogalactan to a yellow cake formulation, however, total quality increased when only 1% arabinogalactan was added. This indicates a self-limiting level in cakes and also addresses the need for further studies at low addition levels of arabinogalactan. In straight dough white breads arabinogalactan slightly decreased volume and increased crumb firmness, however, the use of arabinogalactan was shown to improve dough handling characteristics and the fineness of grain. Arabinogalactan used as a partial replacement for carboxymethyl cellulose in fiber breads resulted in a slight increase in loaf volume and a decrease in crumb firmness. The use of arabinogalactan improved the dough handling characteristics of tortillas, and increased the diameter and spread ratio of cookies. These results indicate that arabinogalactan used at low percentages in baked goods can, under optimized conditions, improve quality, in addition to improving the nutritional value of the baked good due to its soluble fiber content. These advantages need further research to elucidate an optimum response.

Yellow Layer Cakes

The American Institute of Baking (AIB) tested ARABINOGALACTAN F2000 in model yellow layer cakes at 1, 5, and 10%, in accordance with a standard formulation. Cakes and batters containing arabinogalactan were compared to controls for specific gravity, viscosities, internal crumb structure, specific volume, crumb fineness, and total quality. Two series of bakes were conducted. Bake one was conducted to determine proper water levels, and bake two was conducted as an optimization. Results showed that in the series two bake, specific gravities increased in the batter as the percent of arabinogalactan and water increased, while concomitantly, batter viscosities decreased. All batters containing arabinogalactan were lower in viscosity than the control, except in the case where 1% arabinogalactan was used. Specific volumes on all arabinogalactan-containing cakes were lower than the control; however, when 1% arabinogalactan was used specific volumes (3.53 cc/g) were very similar to the controls (3.67 cc/g). The addition of 1%

arabinogalactan produced yellow layer cakes with a total quality score identical to the control cakes; however, a self-limiting level was reached when 5 or 10% arabinogalactan was added. This was possibly due to thinner batter consistency. More research is needed to optimize these formulations around lower additions of arabinogalactan, and to determine the effect of arabinogalactan on cake quality, nutritional attributes, and shelf life.

Straight Dough White Pan Breads

Arabinogalactan was tested in straight dough white pan breads at 0.5, 1.0, and 1.5% based on flour weight at the American Institute of Baking (AIB). Breads were subjectively evaluated for external and internal structure, and for eating characteristics one day after baking. Weights and volumes of all breads were measured one hour after baking, and the internal crumb structure was measured using CrumbScan™. A shelf life study was performed by testing the firmness of the bread crumb at days 1, 3, and 7. Results showed that the volume of the breads decreased slightly with the addition of arabinogalactan in comparison to controls. Breads containing 1% arabinogalactan scored the highest in overall quality, with an improvement noted in better dough make-up qualities and finer grain characteristics. At higher levels of arabinogalactan addition (1.0 and 1.5%) there was a slight tendency for the bread to core. Crumb firmness of the breads increased slightly as storage time increased for all levels of arabinogalactan additions. The total quality scores however, for all levels of arabinogalactan tested were higher than those of the controls due mainly to an improvement in grain fineness, which may be attributed to the film forming properties of arabinogalactan.

Fiber Breads

Arabinogalactan F2000 was tested in fiber breads with or without carboxymethyl cellulose (CMC) by the American Institute of Baking (AIB), in Manhattan, Kansas. The fiber formulations tested included either arabinogalactan alone (0.2%); CMC alone (0.2%); or combinations of arabinogalactan and CMC. The combinations totaled a soluble fiber addition of 0.2% and were: 0.05% AG/0.15% CMC; 0.1% AG/0.1% CMC, and 0.15% AG/0.05% CMC. Breads were subjectively evaluated for external, internal, and eating quality characteristics one day after baking. Weights, volumes, and internal crumb structure of baked breads were measured one hour after baking. The crumb-firming rate and the firmness of the breadcrumb were measured at days 1, 3, and 7 after production. The use of arabinogalactan in combination with CMC resulted in a slight increase of volume. Subjective scores, however, were identical for all breads tested. Breads containing the arabinogalactan also had finer grain

than breads containing CMC alone, although, total quality scores (67.84) were identical for all breads tested. There was a trend noted on all three days of shelf life testing for a slight decrease in crumb firmness when arabinogalactan was used in combination with CMC. However, high standard deviations on these tests made differences difficult to assess. Additional research must be done to optimize both the level of arabinogalactan, and the level of total soluble fiber, which would be optimal for a fiber bread formulation. The improvement in grain structure noted with the use of arabinogalactan may be due to its film forming properties.

Fat-Free Tortillas

Arabinogalactan F2000 was tested in fat-free tortillas at the American Institute of Baking (AIB). Levels of arabinogalactan added to the tortilla formulation were 1, 2, and 5% based on the total flour weight. Tortilla doughs were subjectively evaluated for handling characteristics during both mixing and dough make-up stages. The diameter and stack height of the tortillas were measured one day after gridling, and subjective evaluations were also taken at that time for external, internal, and eating quality. Tortilla stretchability and tearing point were measured on days 1, 6, and 12 after production. Results showed that when arabinogalactan was added at the 2 or 5% level, the tortilla doughs were less sticky and easier to handle at dividing and gridling. However, stack height and diameter of the tortillas decreased with the addition of arabinogalactan compared to the flour controls. Stretchability of the tortillas at each of the arabinogalactan levels was similar to that of the control tortillas except for the 5% level. The addition of 1% arabinogalactan produced tortillas that were softer than the controls at days 1 and 6. However, at the 2 and 5% levels, arabinogalactan incorporation produced tortillas, which were firmer than the controls on day 1, but were less firm than the controls by day 6. Standard deviations of all samples were high making interpretation difficult without further research. The addition of 1-% arabinogalactan produced flour tortillas of similar total quality to the control, while the 2 and 5% addition levels increased total quality scores above those of the control. Stretchability of the arabinogalactan-containing tortillas was identical or similar to the control on the 6th day of storage (12.9 vs 12.8 mm) except when 5% arabinogalactan had been used. These results suggest that arabinogalactan may help to increase consumer acceptability of fat-free tortillas, providing more research is done to optimize the formulations.

Sugar Snap Cookies

Arabinogalactan F2000 was evaluated in sugar snap cookies by the American Institute of Baking (AIB). The soluble fiber was added at 1, 2, and 5% based on the total flour weight of the formulation. The resulting

cookies were subjectively evaluated for production and bake quality characteristics one week after baking. Spread, thickness, spread ratio, and surface cracking on the cookies were also evaluated one week after baking. Results showed that when arabinogalactan was added at the 1 and 2% level, total quality results were similar to the controls. However, when arabinogalactan was added at the 5% level, the dough was slightly softer than the control, indicating a decrease in viscosity. There was a gradual increase in the cookie diameter as levels of arabinogalactan increased and a concomitant decrease in cookie height, thereby increasing the spread/height ratio. The addition of arabinogalactan up to the 2% level decreased the overall quality only slightly in comparison to the control (91.0 vs 89.5 at 1% arabinogalactan). However, cookies produced with 5% arabinogalactan had deficiencies in grain and texture resulting in a score 8.5 points lower than the control. These results indicate a self-limiting level for arabinogalactan in cookies.

Food and Industrial Grade Arabinogalactans in Yellow Cakes

LAREX, Inc. contracted J.S. Williams, Inc. in Plymouth, MN to conduct an experiment with both industrial grade and food grade arabinogalactan in a basic yellow cake formulation. The arabinogalactan was added at the 2% level to the cake mix. All other ingredients remained the same. Cakes were evaluated physically by measuring height, volume, and density. A sensory panel performed subjective evaluations for overall flavor attributes, moistness, mouthfeel, grain, and crumb texture. Results showed that both grades of arabinogalactan improved the moistness of the cakes at day 3, and that the industrial grade arabinogalactan-containing cake was higher and had greater volume than either the control or food grade cake. However the food grade arabinogalactan produced a finer texture, a cleaner mouthfeel, a more desirable color, and a better flavor profile in the cakes than did the industrial grade arabinogalactan.

Improvement of Tablet and Granule Quality with the Use of Arabinogalactan

The Fuji Prefecture Drug Laboratory reported on the use of arabinogalactan to form tablets and granules in their annual report of 1990 [Fuji Prefecture Drug Laboratory, 1990, VOL. 6 TAB 21]. The use of arabinogalactan at the 5% level in a tablet increased the hardness at maximum hardening pressure by 50%. The investigators concluded that arabinogalactan could function as a binder which would aid tablets in resisting breakage. The material apparently also acted as a disintegrating agent, increasing the dissolving property of the tablet in liquid. A 5% addition of arabinogalactan decreased the disintegration time from 7.3 minutes for the blank tablet to 2.9 minutes for the arabinogalactan-containing tablet. Tablet hardness in this experiment was increased from

4.7 kg for the blank tablet to 5.3 kg for the tablet containing arabinogalactan.

In a second study the use of arabinogalactan in granules at 5 and 10% additions was tested for its effect on disintegration time and the degree of abrasiveness. Disintegration time for the control granules was less than 60 minutes, while granules containing 5% arabinogalactan disintegrated in 6.4 minutes, and those containing 10% arabinogalactan disintegrated in 2.0 minutes. Both levels of arabinogalactan reduced the abrasiveness of the granules from 0.76% for the control to 0.5% for the arabinogalactan variables. Investigators concluded that arabinogalactan-containing granules showed the same effectiveness as in tablets, in that it greatly improved the dissolving property of the granules.

G. Functionality

Arabinogalactan-Protein as a Wine Protein Haze Reducer

In a report by Waters, et al., 1994, the authors stated that red and white wines contain a complex mixture of colloids. Of the wine polysaccharides, some originate from yeast, while others are grape-derived and composed of arabinose and galactose. The majority of grape-derived wine polysaccharides are arabinogalactan-proteins. This class of colloids, which has been found in flowering plants from every taxonomic group tested, contains a high proportion of carbohydrates and usually less than 10% by weight of protein according to the authors. The authors reported that the presence of protein is of concern to the wine maker because wine proteins are inherently unstable and can either aggregate and subsequently precipitate to give an amorphous sediment, or flocculate and thus produce a suspended and unattractive haze. In this study, the authors reported that a wine arabinogalactan-protein was capable of reducing the visible hazing of proteins in wine below those of a control when added at 200 μg/ml [Waters, et al., 1994, VOL. 8 TAB 20].

Emulsifying Action of Arabinogalactan

According to Nazareth, et al., in 1961, Larch arabinogalactan is a good emulsifier forming stable, low-viscosity emulsions. In their study a series of liquid petrolatum emulsions were made with arabinogalactan and with gum acacia using the following proportions of oil, water, and gum: 4:2:1, 6:3:1, and 8:4:1. These emulsions were made in a Waring blender and then diluted to contain equal parts of water and oil. The emulsions made with the arabinogalactan were reported to be less viscous compared to the ones made with gum acacia. As an example, the final emulsion using a 4:2:1 ratio of oil, water, and gum, had a viscosity of 46 cps. When

arabinogalactan was used as measured by a Brookfield Synchro-lectric Viscosimeter, Spindle No. 1, at 12 rpms. These results could be compared to 600 cps. using spindle No. 3 for a similar gum acacia emulsion. An 8-week stability study on the globule size at 4⊕C, room temperature, and 50⊕C showed no difference between the two sets of emulsions. The authors indicated that it was expected when a slight increase in globule size at 4⊕ and 50⊕C was evident in both sets of emulsions. Globule size however, did not increase drastically, since the initial values reported were 4 microns in both emulsions, and the final values at 4⊕ and 50⊕C were 5 microns. The authors concluded that arabinogalactan was therefore as capable of making stable emulsions as gum acacia, but might be of more value where emulsions of low viscosity were desired [Nazareth, et. al., 1961, VOL. 7 TAB 9].

Product Development with Arabinogalactan

Numerous patents ranging over a 35 year period from 1962 to 1997 were identified which covered product development with arabinogalactan and related compounds (See Table 2). These patented processes or compositions utilized a range of functional properties attributable to arabinogalactan, including its use as a film-former, foam adhesion additive, thickener, bulking agent, emulsifier, and therapeutic agent.

Table 2: Functional Aspects Of Arabinogalactan Utilized In Product Development

Functional Aspect	Level Used	Reference
Bulking Agent with Artificial Sweeteners		
1. To replace the bulk and viscosity of sugar	35% in Low-Calorie Maple Syrup 96% of a Sugar substitute 57% in Uncooked Fudge 85% in Butter Icing 64% in Chocolate Syrup 35% in Syrup Base	U.S. Patent No. 3,294,544 VOL. 7 TAB 20
Aqueous Phase Emulsifier		
To provide an inner aqueous phase in a w/o/w emulsion for a dressing	7% dry weight basis	U.S. Patent No. 4,632,840 VOL. 8 TAB 2
Emulsifier		
Emulsifying action for a cream/alcohol beverage	--	U.S. Patent No. 4,419,378 VOL. 7 TAB 25
Thickener		
1. To provide a hydrophilic polymer with a low viscosity for an almond nut paste for beverages and desserts	7 % dry weight basis	U.S. Patent No. 4,639,374 VOL. 8 TAB 3
2. To provide a thickening agent	1.2% in a nougat confection	U.S. Patent No. 4,714,620 VOL. 8 TAB 4
3. To provide a bulking agent with low bulk density	3-15%	U.S. Patent No. 3,704,138 VOL. 7 TAB 22

Reduction in After-Taste		
1. To modify the taste of artificial sweetness	< 2.5% of the final product	U.S. Patent No. 4,228,198 VOL. 7 TAB 24
Film-Former		
1. Encapsulating coating for flavors	3-6 parts by weight to the flavorant	U.S. Patent No. 3,264,114 VOL. 7 TAB 19
2. Edible Film	10-20% of an aqueous solution which is dried to ○ 25% moisture	U.S. Patent No. 5,089,307 VOL. 8 TAB 9
3. Film-former for browning composition	0.01-1.0% of a browning composition	U.S. Patent No. 5,139,800 VOL. 8 TAB 12
Bulking Agent		
1. To provide a partially non-digestible bulking agent for a low-calorie, low-fat chocolate confectionery	25-60%	U.S. Patent No. 4,810,516 VOL. 8 TAB 5
2. To provide a tasteless bulking agent for an adhesive sweetening mixture for nuts	--	U.S. Patent No. 5,194,278 VOL. 8 TAB 13
3. To provide a gum-type bulking agent for a "slush" partially frozen beverage	< 1%	U.S. Patent No. 1,331,518 VOL. 7 TAB 17
4. To provide bodying and bulking agent for reduced calorie candy	11-28% as a replacement for fat and sweetened condensed skim milk	U.S. Patent No. 3,800,045 VOL. 7 TAB 23
Stabilizing Agent		
1. Stabilizing Agent for aspartame in chewing gum	--	U.S. Patent No. 4,828,857 VOL. 8 TAB 6
2. To provide a stabilizer with at least 4 monosaccharide units as a preventative agent against browning	40% of a solids composition	U.S. Patent No. 4,547,377 VOL. 8 TAB 1
Component of Sugar Substitutes		
1. To provide a derivative for a novel sweetening compound	--	U.S. Patent No. 5,041,541 VOL. 8 TAB 8
Gum Product		
To provide a cultured gum substitute for gum arabic	--	U.S. Patent No. 5,133,979 VOL. 8 TAB 11
Foam Adhesive		
As a foam improver in beer containing chemical preservatives	40 ppm	U.S. Patent No. 3,443,957 VOL. 7 TAB 21

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Section III: Analytical Method for Arabinogalactan

Arabinogalactan can be meaningfully characterized by molecular weight. LAREX, Inc. currently utilizes a molecular weight method based on High Pressure Liquid Chromatography-Gel Permeation Chromatography (HPLC-GPC) to detect the presence of arabinogalactan. A procedure is presented for the molecular weight determination at TAB 1.

Section IV: Arabinogalactan: Its Safety when Consumed as an Ingredient in Processed Food

Introduction

LAREX, Inc. extracts and processes arabinogalactan from the butt cuts of logs of the genus *Larix* at its manufacturing plant in Cohasset, Minnesota. The manufacturing plant operates under cGMP, and all raw materials utilized in processing of the arabinogalactan are food grade. A HACCP program and a recall a program are in place to assure that the food grade status of the arabinogalactan products is maintained, and that each production lot is trackable. Based on the food grade status of its manufacturing plant, and the fact that the safety of arabinogalactan is supported by numerous studies in the published literature, LAREX believes that its arabinogalactan product is safe and suitable for use in food ingredients.

A. Arabinogalactan Description

Arabinogalactans belong to a major carbohydrate group called hemicelluloses, which are abundant in the primary and secondary cell walls of plants that have undergone lignification. Within the cell walls they form an aqueous gel in which bundles of cellulose microfibrils are embedded in regular or irregular orientations [Whistler, et al., VOL. 11 TAB 16 and Wilke, 1983, VOL. 11 TAB 17]. Isolated arabinogalactan has been reported to be composed of a major, highly branched β galactan fraction with a molecular weight of approximately 100,000 and a minor β galactan fraction with a molecular weight of approximately 16,000 in a 4:1 ratio [Wilkie, 1983, VOL. 11 TAB 17].

Man has had a long history of natural arabinogalactan consumption. Arabinogalactans are consumed regularly in many plant foods, including fruits, wheat flour, and other woody plant exudates [Chen, et al., 1994, VOL. 10 TAB 5, D'Appolonia, 1980 VOL. 10 TAB 10, BeMiller, 1989, VOL. 10 TAB 2, and Wilke, 1983, VOL. 11 TAB 17]. Arabinogalactans often enter the human food chain as arabinogalactan-proteins. These complexes are widely distributed in plants and are believed to play a role in plant cell development. They are constructed with a protein backbone, which is rich in hydroxyproline. This protein component accounts for approximately 2-10% of the molecule, while the remaining 90% is a carbohydrate fraction composed of a highly branched arabinogalactan [Chen, et al., 1994, VOL. 10 TAB 5].

B. Arabinogalactan From Western Larch

Arabinogalactan has also been known as Larch gum and is extracted from the Western Larch tree. The gum was first reported in 1898, but successful commercial production did not begin until the late 1960's. Larch gum is similar to gum arabic in that it is extremely soluble, and solutions of high concentration (up to 50%) can be produced with very low viscosities [CRC Handbook of Food Additives, 1972, VOL. 10 TAB 7]. Arabinogalactan occurs in concentrations ranging from 5-30% on a dry weight basis in the heartwood of many species of *Larix*, which is a deciduous conifer, native to the temperate and sub-arctic zones of the Northern Hemisphere [BeMiller, 1989, VOL. 10, TAB 2]. The gum naturally exudes as a result of injuries and subsequently collects under the bark [BeMiller, 1989, VOL. 10, TAB 2 and CRC, 1972, VOL. 10 TAB 7]. The largest amounts of arabinogalactan occur in *Larix occidentalis, which* is presently the sole commercial source in the United States. Other species of *Larix* such as *Larix laricina*, the tamarack, also contain high concentrations of arabinogalactan.

The original commercial production was based on the extraction of wood chips, which remain a by-product of the lumber industry today. The yield of extractable gum depends upon the part of the tree from which it is extracted. The lower part, or the butt cut of the Western Larch provides the current commercial source for extraction, since this section of the tree is favored neither for lumber nor for pulping. According to earlier literature, Larch gum was not extensively used during the 1960's and 70's, presumably because it was not economically feasible, although various authors have stated that Larch gum could very likely be used as a substitute for gum arabic [CRC, 1972, VOL. 10 TAB 7 and BeMiller, 1989, VOL. 10, TAB 2].

In the present process developed by LAREX, Western Larch wood is debarked, chipped, and then extracted with hot water in a two-stage extraction process equipped with screw presses. The extractant is purified, concentrated, and diverted to one of several product streams [LAREX, 1997, VOL. 11 TAB 5]. The first product to be developed from the extraction process is a liquid having a concentration of about 50% arabinogalactan. This product can be preserved with a small amount of potassium sorbate, and can then either be sold as a food ingredient, or as an industrial processing aid. For certain food applications the liquid product is further purified with food grade hydrogen peroxide, and potassium hydroxide to improve color, taste, and aroma. Optionally, these highly purified and decolorized products may be spray dried before entering the food ingredient market [LAREX, 1997, VOL. 11, TAB 5].

Larch arabinogalactan has been reported as an effective flavor fixative with superior qualities to gum arabic since it does not have a tendency to react with proteins such as gelatins. It is also an effective low caloric value bulking agent, and a valuable source of soluble fiber [BeMiller, 1989, VOL. 10 TAB 2].

C. Food Additive Petition

In the early 1960's Stein Hall and Company, Inc. and St. Regis paper company jointly submitted a food additive petition to the Food and Drug Administration asking that arabinogalactan, extracted from Western Larch (*Larix occidentalis* Nutt.) be approved for use in foods as an emulsifier, stabilizer, binder, and bodying agent. This petition was subsequently granted by the Food and Drug Administration in 1965 [Federal Register, 1965, VOL. 10 TAB 14]. The product described in this food additive petition was offered to the industry under the name "Stractan". The extraction process for this product consisted of subjecting wood chips to water ranging from ambient temperatures to 150#. The extraction procedure was carried out by counter current leaching and the concentrated liquor was then dried to a yield a light tan powder [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15].

The petition submitted to FDA contained reports from several safety studies, chemical characterizations of the product, a report on the structure of several related compounds, limited data on the technical effects of arabinogalactan, and data on the determination of its molecular weight [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15]. The petitioners reviewed the safety studies included in the petition, and concluded, based on the fact that high levels of arabinogalactan had been fed with no ill effect, that arabinogalactan should be considered safe as a food ingredient, and that no tolerance level need be set. Various publications have indicated that the petitioners were interested in positioning arabinogalactan as a substitute for gum arabic at the time they submitted the petition, and consequently did not envision that arabinogalactan could have broader use as a food ingredient [CRC, 1972, VOL. 10 TAB 7 and, Anderson, 1966, VOL. 3 TAB 2].

The petition was subsequently approved for use in foods as an emulsifier, stabilizer, binding or viscosity agent for essential oils, flavors, non-nutritive sweeteners, salad dressings, and pudding mixes. The notice of its approval as a food additive was published in the Federal Register on February 25, 1965 as § 121.1174 [Federal Register, 1965, VOL. 10 TAB 14].

D. Safety Studies

Stein, Hall and Company conducted several safety and feeding studies utilizing relatively high levels of arabinogalactan in test diets in support of their food additive petition. These studies were considered by FDA prior to issuing the food additive regulation.

Acute Toxicity Study

Washington State University conducted an acute toxicity study in rats. In a series of experiments with 108 adult male albino rats, in which arabinogalactan was administered intraperitoneally as an aqueous solution, the investigators found an LD_{50} of approximately 12.9 g/kg. Statistical treatment of the data indicated a high degree of confidence in that value [Nazareth, et al., 1961, VOL. 11, TAB 9].

Eight Week Feeding Study

The same group of researchers also conducted and 8-week feeding study with rats, in which groups of male and female rats were fed diets containing 0%, 2%, 10%, and 20% arabinogalactan. The authors noted that the animals consuming the higher percentages of arabinogalactan ate a larger amount of food, but showed slightly lower weight gain. This observation led the authors to state that they saw no evidence of any particular nutritional value on the part of arabinogalactan. However, it was noted at the time, that the animals consuming the highest levels were more lively, and had a smoother coat than animals consuming the lower levels [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15].

Thirty-Day Preliminary Toxicity Study

A third study was designed as a 30-day preliminary toxicity study with rats, in which groups of 10 male and 10 female weanling rats were fed diets containing 0, 2, 10, or 25% arabinogalactan. A slight diarrhea was noticed in the 25% group, however, this did not interfere with growth, and weight gain was relatively uniform in all groups [Nazareth, et al., 1961, VOL. 11 TAB 9]. Necropsy and tissue sections of the animals at the end of the study revealed no gross lesions of any significance associated with the feeding of arabinogalactan. A complete examination of the blood after the sacrifice of the animals gave variable results in all groups, including the control, but the authors stated that these variations were probably normal for the age and strain of rat. The conclusions drawn from these preliminary, short-term studies indicated that arabinogalactan was innocuous to rats when fed for 30 days at up to 25% of their ration [Nazareth, et al., 1961, VOL. 11 TAB 9].

Caloric Value Studies

Included in the food additive petition were two caloric value studies conducted by the Wisconsin Alumni Research Foundation in 1963 and 1964. In determining the caloric value of arabinogalactan, the researchers used weanling male rats. The animals were provided a basal ration at a level of 5 g per rat per day. In a one week test period, involving 7 groups of 5 rats, test samples of Stractan 10 or corn starch were fed at levels of 0.5, 1, and 2 g per rat per day, or approximately 9, 17, and 29% of the daily ration.

The researchers noted that two groups of rats receiving Stractan 10 at the 17 and 29% levels per day respectively, developed severe diarrhea the second day of supplementation, which remained during the entire test period. Researchers felt this accounted for a lower gain among these groups. However, Stractan 10 fed at the 0.5 gram per day or 9% level in the ration was well tolerated and, was found to have about 30% of the caloric value of corn starch [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15].

In a second caloric study, male rats were divided into 5 groups of 6 rats. Test groups were supplemented for one week with Stractan 10 or cornstarch at levels of 1 and 3 grams per rat per day. Results showed that rats consuming Stractan 10 at the 1 gram per day level gained 3.7 grams over the study, whereas rats consuming the basal control diet, and rats consuming 1 gram of corn starch gained 8.1 and 8.0 grams respectively. The rats consuming 3 grams of Stractan 10 per day lost 14 grams during the period [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15].

Six-Month Chronic Toxicity Study

A six-month chronic toxicity study with Stractan products numbers 10 and 15 was conducted in beagle dogs by the Wisconsin Alumni Research Association in 1964. Beagle dogs were divided into 8 groups of 2 males and 2 females each. The test materials were added at 1, 5, and 10% of a commercial dog food, which constituted the control ration. A negative control containing no arabinogalactan and a positive control containing bran cellulose at the 10% level were also included in the study design. Weekly body weights and food consumption levels were kept for the entire period. At the end of 6 weeks, because animals receiving Stractan 15 were performing satisfactorily, a decision was made to terminate the groups receiving Stractan 10.

Initial clinical tests were conducted on all animals in all groups. At the end of the 6 month period all animals were sacrificed and examined for any

gross clinical signs. Organs were weighed and tissues for histological studies were collected. Body weight data indicated a slight depression of body weight gains for male animals in both the test and positive control groups in comparison to the negative control animals. There was no significant variation in the clinical data between the negative control and the test animals, and no significant gross or histological alterations were noted. The researchers concluded that at 90 days and at 6 months, no indication of toxicity was noted in animals receiving diets containing 1, 5, or 10% of Stractan 15 or in animals receiving 10% bran cellulose. The researchers added that weight variations in the males in this study appeared to have been the result of decreased palatability and caloric value [Food Additive Petition No. 5A1563, 1964, VOL. 10 TAB 15].

Utilization of Arabinogalactan by Pigs

In a later study Froseth, et al, reporting in 1972 conducted two studies to determine the utilization of arabinogalactan by growing pigs as a guide to its utilization by humans. In the first study, groups of 6 pigs were allotted to each of 3 dietary treatments and a fourth group was slaughtered at the beginning of the trial for carcass evaluations. The remaining animals were fed diets for 63 days in which 0, 10, and 20% arabinogalactan replaced cerelose. The authors noted that pigs fed the 20% arabinogalactan diet had leaner and meatier carcasses, and they postulated that this was at least partially due to the slightly lower daily net energy of gain intake by the animals fed the highest level of arabinogalactan. The net energy gain content of arabinogalactan was more than 4 times higher (1.713) when arabinogalactan was included as only 10% of the diet as compared to its inclusion at 20% of the diet (0.392). The results showed that the net energy of gain content of arabinogalactan when included at the 10% level was nearly equal to the basal ration components, which were predominantly corn, soy bean meal and cerelose sugar. The average daily feed consumption per pound of gain was 3.09 for the control diets, 3.03 for the 10% arabinogalactan diet, and 3.38 for the 20% arabinogalactan diet. The energy gain in Kcal/g of ration dry matter consumed was found to decrease with increasing dietary arabinogalactan. The gain in Kcal/g of ration dry matter was 1.760 for the control, 1.755 for the 10% arabinogalactan diet, and 1.451 for the 20% arabinogalactan diet [Froseth, et al., 1972, VOL. 10 TAB 16].

The high net energy gain content of arabinogalactan at the 10% level (3,965.8 Kcal/day) was consistent with the high level of swine performance, feed consumption, and carcass characteristics noted by the investigators. The authors concluded that arabinogalactan was highly digestible and well utilized at the 10% dietary level. They speculated however, that it was possible that a low dietary level of arabinogalactan

may have increased the digestibility and utilization of the other components of the ration. The low net energy of gain content of arabinogalactan at the 20% dietary level (3,713.0 Kcal/day) was also consistent with the animal performance parameters observed. The authors indicated that this dietary level of arabinogalactan was either poorly digested and/or poorly utilized by the pig. However, at the 10% level positive associative effects may have effected the net energy of gain [Froseth et al., 1972, VOL. 10 TAB 16].

In a second metabolism trial, 8 pigs weighing 30 kg were assigned to one of two replicates of a 4 x 4 Latin square. Rations evaluated contained 0, 10, 20, or 30% arabinogalactan, and iron oxide was used as a fecal marker to indicate the beginning and end of each collection period. Pigs were given a 5 day adjustment period in metabolism crates and collection periods lasted 4 days. Results showed that percent digestibility of the ration dry matter and of the arabinogalactan decreased with an increase in dietary arabinogalactan. The decrease was very slight at the 10% level, but was much greater at the 20 and 30% arabinogalactan levels. Digestibility for arabinogalactan was 83.7% at the 10% level, 83.4% for the 20% level, and 57.2% for the 30% level. Digestible energy and metabolizeable energy content of the ration dry matter also decreased with increasing dietary arabinogalactan. Digestible energy in Kcal/g of the ration dry matter was 3.873 for the control, 3.810 for the 10% arabinogalactan level, 3.502 for the 20% arabinogalactan level, and 3.425 for the 30% level. The authors concluded that while arabinogalactan may not be as high in usable metabolizeable energy as table sugar, or starch, it was certainly well utilized and comparatively high in metabolizeable energy for swine, especially when included in the diet at low levels [Froseth, et al., 1972, VOL. 10 TAB 16].

E. Arabinogalactan Fermentation by Human Fecal Bacteria

A number of researchers have investigated the utilization of arabinogalactan by human colonic bacteria [Mazur, et al., 1993, VOL. 11 TAB 8; Crociani, et al., 1994, VOL. 10, TAB 8; Englyst, et al., 1987, v 10 TAB 12; Salyers, et al., VOL. 11 TAB 12; Macfarlane, et al., 1995, VOL. 11 TAB 7; and Vince, et al., VOL. 11 TAB 15]. These studies demonstrated that arabinogalactan was fermented in the human colon by the indigenous bacterial population. The fermentation rate was found, in general to be slower than for other carbohydrates because of its highly branched structure. However, one author showed that the branched chains of arabinogalactan were co-utilized with the backbone sugars. Arabinogalactan was fermentable to the short-chain fatty acids necessary for the nourishment of human colonic epithelium. A source of arabinogalactan was shown to induce the enzymes necessary for its

degradation. Finally, arabinogalactan was shown to reduce the level of ammonia absorption from the colon.

As evidence of the continual consumption of arabinogalactans by humans, Mazur, et al., 1993, found that arabinogalactans were fermentable by human colonic flora [Mazur, et al., 1993, VOL. 11, TAB 8]. The authors classified arabinogalactan as a slowly fermentable carbohydrate. Their study found that highly branched polysaccharides exhibited consistently lower rates of metabolism than did linear, tetra, penta, or polysaccharides. The authors suggested that the branching of the arabinogalactan might hinder access of glycosidases to glycosidic linkages [Mazur, et al., 1993, VOL. 11 TAB 8]. Crociani, et al., 1994, confirmed that arabinogalactan was degraded by 17 out of 20 strains of *Bifidobacterium longus* (a common bacterium of the human colon) [Crociani, et al., 1994, VOL. 10 TAB 8].

A study published by Englyst, et al., 1987, investigated the polysaccharide-degrading activity in different fractions of human feces and found that non-starchy polysaccharides, including arabinogalactan, were fermented by mixed populations of human fecal bacteria in batch culture [Englyst, et al., 1987, VOL. 10 TAB 12]. Detailed carbohydrate analysis demonstrated that starch and pectin were the most rapidly degraded substrates, and that arabinogalactan and xylan were broken down more slowly. Time course measurements of the polysaccharides in the batch culture fermentation showed that the arabino side chains of pectin, xylan, and arabinogalactan were co-utilized with the backbone sugars. The authors found that molar ratios of the short-chain fatty acids produced, including acetate, propionate, and butyrate were dependent on the polysaccharide tested. For arabinogalactan they were 50:42:8, respectively. Interestingly, the presence of starch did not inhibit the breakdown of arabinogalactan, xylan or pectin by fecal bacteria [Englyst et al., 1987, VOL. 10 TAB 12].

Englyst, et al., 1987, discussed the importance of large gut fermentation in human physiology, since volatile fatty acids are sufficiently absorbed from the colon to provide a substantial portion of energy for the host. The authors indicated that volatile fatty acids also stimulate salt and water absorption, and are important contributors to intermediary metabolism in the colonic epithelium. In the liver, propionate may influence gluconeogenesis and cholesterologenesis. The authors concluded that carbohydrate fermentation by the intestinal microflora could be regarded as an important process controlling many aspects of large bowel function in man.

In this study fresh feces from 5 individuals who had been eating normal western diets were suspended in anaerobic medium at pH 6.5 to produce 10% w/v fecal slurries. Each slurry was then centrifuged to yield a washed

bacterial cell fraction, a particulate fraction, and a cell-free supernatant fraction. To test polysaccharide fermentation by mixed bacterial populations, fecal samples were obtained from 2 individuals and washed fecal bacteria cells were prepared as described above. Results of the fermentation studies showed that the rate of hydrolysis of the polysaccharide was found to be the rate-limiting step in the utilization of arabinogalactan. In addition, results demonstrated that the arabino side chains and galactose backbone of arabinogalactan were simultaneously degraded by colonic bacteria. In the Englyst study about 43% of the polysaccharide fermented was recovered as volatile fatty acids [Englyst, et al., 1987, VOL. 10 TAB 12].

In a study published in 1981 by Salyers, et al., continuous cultures were used to approximate some of the conditions encountered by colon bacteria in their normal habitat. The authors stated that to their knowledge, this study represented the first attempt to investigate polysaccharide breakdown by anaerobic bacteria in continuous culture. To determine the effect of very slow growth rates, the authors equilibrated bacteria at steady-state growth rates of 3.5, 6.3, 11.6, and 27.7 hours per generation. At each growth rate the bacterial yield was determined and used as an indication of how efficiently the bacteria were using arabinogalactan. The ability of the bacteria to produce enzymes for degrading a new carbohydrate source was determined by measuring the rate at which α-glucosidase an inducible enzyme was produced when bacteria were exposed to maltose. In this study the spent medium was analyzed to determine whether any undegraded portions of the arabinogalactan remained. Growth rates of the organisms tested were found to be on the order of 10 hours per generation or longer.

Results of this investigation showed that the concentration of viable bacteria in the culture vessel (1.7 - 1.9 x 10^9/ml) was the same at all dilution rates. Viability was approximately 100% since the total concentration of bacteria, as determined using a counting chamber, was 1.8 x 10^9/ml. Despite high viabilities, total cellular carbohydrate declined, as growth yields became slower. The author stated that this might reflect a decrease in storage polysaccharides [Salyers, et al., 1981, VOL. 11 TAB 12].

Several conclusions could be drawn from the results; first, that growth yields on arabinogalactan were quite high, and were comparable to yields obtainable when a monosaccharide, such as glucose or galactose was the substrate. The affinity of *Bacteroides thetaiotaomicron,* the test organism, for arabinogalactan was much lower than its affinity for galactose as indicated by the fact that the concentration of unutilized substrate increased much more rapidly with the increasing growth rates when

arabinogalactan was the substrate. The authors cautioned that when dietary fiber components are degraded by colonic bacteria the original set of polysaccharides may be replaced by a different mixture of polysaccharides and oligomers, and the properties of this new mixture, for instance the ability to bind ions or toxic substances, may be very different from the properties of the original mixture. In conclusion, the ability of the organisms tested to produce the enzymes necessary to enable them to switch to a new carbohydrate source was significantly decreased when generation times were long [Salyers, et al., 1981, VOL. 11, TAB 12].

The objectives of a study by Macfarlane, et, al., 1995, were to investigate whether *Bifidobacterium adolescentis* was able to compete in carbon-limited continuous culture with *Bacteroides* species for the plant cell wall polysaccharide arabinogalactan, and to determine the effects of pH and growth rates on interactions between these two organisms, since those parameters are important environmental, and physiological variables of the colon [Macfarlane, et al., 1995, VOL. 11 TAB 7]. Measurements of residual carbohydrate in pure and mixed culture chemostats showed that the *Bacteroides* species extensively digested the galactose backbone of the polymer, and to a lesser degree, the arabino side chains. Nevertheless, arabinose monomers and oligosaccharides accumulated in these cultures under all growth conditions. *Bifidobacterium* utilized considerably less arabinogalactan than did *Bacteroides*, as was reflected in the mixed culture studies. These experiments demonstrated that *Bacteroides thetaiotaomicron* was able to compete more successfully for the cell wall polysaccharide than *Bifidobacterium adolescentis* under conditions broadly similar to those encountered in the human colon. The study indicated the existence of syngeristic interactions between the two organisms that were growth rate dependent [Macfarlane, et al., 1995, VOL. 11 TAB 7].

Vince et al., 1990 reported that they had developed an *in vitro* method of stool incubation, which could be used to study the metabolic activity of intestinal bacteria. In their system the disaccharide lactulose was metabolized with the production of large amounts of short-chain fatty acids and a marked decrease in bacterial formation of ammonia. The aim of their study was to compare the influence of four carbohydrates, lactulose, pectin, arabinogalactan, and cellulose on the production of short-chain fatty acids and ammonia. They proposed to determine whether previous exposure to increased amounts of these substrates significantly altered bacterial metabolism in the gut [Vince et al., 1990, VOL. 11 TAB 15].

Fecal samples were obtained for inocula from subjects before and after they had ingested more than twice the normal dietary amounts of each substance. Five healthy subjects age 27-56 years and weighing 44-83 kg

were studied, first while taking their usual diets, and later while eating their usual diets with the addition of the various carbohydrates listed above. Pectin and cellulose were taken in a dose of 0.3 g/kg per day, and lactulose and arabinogalactan were taken in a dose of 0.8 g/kg per day. For the fermentation studies, five equal 10-100 ml portions of fecal homogenate were placed in incubation vessels, and four vessels were supplemented with 10 g/l of either lactulose, cellulose, arabinogalactan, or pectin [Vince et al., 1990 VOL. 11 TAB 15].

Two of the five subjects consumed their extra dietary carbohydrates for 14 days, with their feces being studied after days 2, 7, and 14. Because the observed effects of short-chain fatty acid production and ammonia metabolism were no greater after day 7 or 14, than after day 2, the remaining subjects were studied only after the second day. When additional carbohydrate had not been eaten, propionate and butyrate were present in approximately equal concentrations at zero hours and 48 hours as well as in the unsupplemented control incubates. After excess carbohydrate had been eaten, butyrate exceeded propionate in all incubates, both unsupplemented and supplemented [Vince et al., 1990 VOL. 11 TAB 15].

The concentration of ammonia increased steadily during incubation, in all samples except those supplemented with lactulose. Results from unsupplemented control incubates showed that ingestion of extra carbohydrates did not reduce net ammonia generation significantly at any of the individual sampling times; but, when 0, 1.5, and 3 hour results were pooled, significantly less ammonia was generated in incubates from subjects who had eaten lactulose or arabinogalactan. Results showed that only lactulose, pectin, and arabinogalactan were fermented vigorously. Those three carbohydrates produced very similar amounts of short-chain fatty acids within 48 hours. In this study the butyrate concentration usually exceeded that for propionate, especially after addition of fermentable carbohydrate. The authors proposed that if similar changes occurred in the intact large intestine after ingestion of fermentable carbohydrates, these might be of clinical benefit because butyrate is an important metabolic fuel for colon epithelial cells. The authors stated that pectin and arabinogalactan were normal dietary constituents being present as structural polysaccharides in plant cell walls. The authors postulated that arabinogalactan might have some value in the treatment of porto-systemic encephalopathy, since it would tend to lower ammonia absorption without the drastic side effects which might accompany the use of lactulose [Vince et al., 1990, VOL. 11 TAB 15].

F. <u>Assay for Mutagenicity</u>

In order to test the mutagenicity of its arabinogalactan product, Larex, Inc. subjected a test sample to a *Salmonella*/microsome assay. The assay was performed using the standard plate incorporation procedure with several *Salmonella typhimurium* strains. These assays were done both in the presence and absence of an Aroclor 1254 induced rat-liver metabolic activation system. The conclusion drawn from the study was that no mutagenicity was found under the test conditions used, which included dose levels ranging from 156 - 5,000 μg/plate [Winegar, 1996, VOL. 11 TAB 18].

G. Neutral Red Uptake Bioassay

A Neutral Red Uptake Bioassay was used to assess the toxicity of arabinogalactan to normal human epidermal keratinocytes (NHEK). The Neutral Red Uptake Bioassay is used to quantitatively measure the toxicity of a test material to NHEK cultures by comparing the neutral red dye uptake of test material-treated NHEK cultures to the neutral red uptake in control solvent (sodium lauryl sulfate) treated cultures. Results showed that the NRU_{50} for arabinogalactan was 3,650 μg/ml. These results indicated that arabinogalactan showed toxicity only when administered at levels which were more than two orders of magnitude higher than the positive control (4.18 μg/ml) [Harbell, et al., 1996, VOL. 11 TAB 1].

H. Arabinogalactan and Insulin Response

Ambrus et al., 1977 conducted a study whose purpose was to investigate the question of the effect of sweet taste on insulin secretion and blood sugar levels using a variety of sweet tasting compounds including calorigenic agents such as galactose, and non-calorigenic sweeteners such as saccharin and arabinogalactan. Twenty male patients between the ages of 25 and 50 participated in this study. All subjects were fasted for 12 hours before each experiment. On a double blind randomized basis the patients were given either 40 g of galactose, 50 g of arabinogalactan with 0.11 g of sodium saccharin, 2 g of methyl-cellulose with 0.083 g sodium saccharin, or 4 grams of galactose. All solutions were flavored and were given in 200 ml of distilled water orally [Ambrus, et al., 1977, [VOL. 10 TAB 1].

The authors stated that combinations of arabinogalactan with small amounts of sodium saccharin exhibited the flavor and bulk of powdered sugar, and it is for this reason that it was used as a sugar substitute. None

of the sweetening agents induced significant changes on plasma insulin or glucose levels.

I. Current Safe Use of Arabinogalactan

Arabinogalactan is approved as a food additive at 21 CFR §172.230 and §172.610 [Federal Register, 1965 VOL. 10 TAB 14]. It has been listed as a GRAS ingredient by the Flavor Extract Manufacturer's Association since 1972 [Oser, et al., 1972, VOL. 11 TAB 10]. It is also listed as a food additive in Canada and Japan [LAREX, 1997, VOL. 11 TAB 5].

Section V: Environmental Assessment

The LAREX, Inc. manufacturing plant for arabinogalactan products is located in Cohasset, Minnesota. It is the position of LAREX, Inc. that the manufacture of its products poses no threat to the environment. All manufacturing is performed under cGMP, and any waste materials from the plant are disposed of through proper channels. All liquid waste from the plant is disposed of through the Cohasset, Minnesota City sewer system, and solid waste from the plant is sold to secondary end users or sent to an appropriate landfill facility.

To further establish that the production of arabinogalactan poses no threat to the environment, LAREX, Inc. subjected its arabinogalactan product to a OECD screening test for biodegradability [BioScreen Testing Services, Inc. Report, 7/10/96, VOL. TAB 1]. Results showed that the arabinogalactan material obtained greater than 70% dissolved organic carbon (DOC) removal within 28 days (the required level for a valid test). The loss of dissolved organic carbon from the arabinogalactan sample was above the 70% level at day 17, and remained above that level for the duration of the 28 day test. The conclusion from this experiment was that arabinogalactan can be regarded as readily biodegradable.

of the sweetening agents induced significant changes on plasma insulin or glucose levels.

I. Current Safe Use of Arabinogalactan

Arabinogalactan is approved as a food additive at 21 CFR §172.230 and §172.610 [Federal Register, 1965 VOL. 10 TAB 14]. It has been listed as a GRAS ingredient by the Flavor Extract Manufacturer's Association since 1972 [Oser, et al., 1972, VOL. 11 TAB 10]. It is also listed as a food additive in Canada and Japan [LAREX, 1997, VOL. 11 TAB 5].

Section V: Environmental Assessment

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Section I: Chemical Identity of Arabinogalactan
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CH

LAREX, Inc.

Arabinogalactan

GRAS Report

Presented to

United States Food and Drug Administration

March 19, 1998

History of Arabinogalactan (AG)

- Identified by paper industry as a "hindrance"
- First commercial extraction in 1960's by St. Regis Paper (Montana)
- Initial manufacturing capacity/applications limited
- Commercialization of AG not strategically appropriate
- Champion abandons AG project
- Montana/Minnesota connection for reviving AG

LAREX. 1

Larex Incorporated

- Founded in St. Paul, MN, 1994
- AG stock purchased from St. Regis Paper
- Began construction of >8 million lbs/yr production facility
- Exclusive manufacturers of Arabinogalactan (AG)
- Wide range of applications: Food/Beverage, Personal Care, Printing, Biomedical, Pharmaceutical, Animal Feed

LAREX. 2

MANAGEMENT TEAM

- Michael L. Finney, President & CEO
- Robert (Bo) Nickoloff, COO
- Richard N. Faulkner, VP of Manufacturing
- Richard Lamb, Director of Process Technology
- Timothy J. Werth, Director-Sales & Marketing
- Mark D. Fandrich, Controller

LAREX. 3

VISION

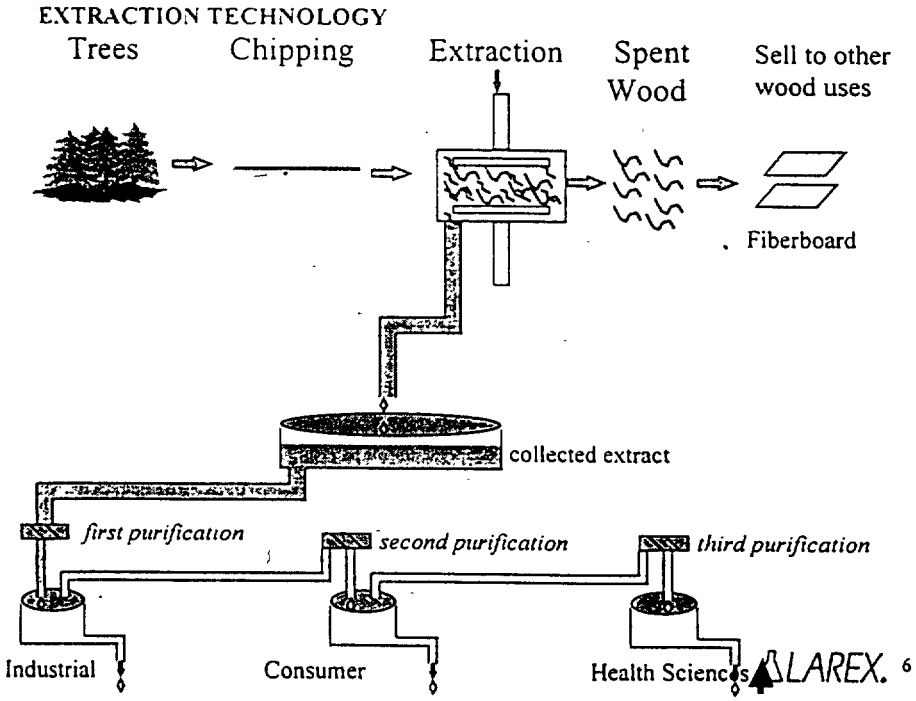
Larex will be recognized as the global commercial scale processor of value-added natural compounds derived from trees.

LAREX. 4

MILESTONES ACHIEVED

- Products in the market (Late 95-St. Regis AG)
- Larex manufacturing facility complete-first product sold to food segment (Jul 96)
- Patent applications filed
- Distributor network in place
- Raw material network in place
- AIB certified manufacturing plant (11/97)

LAREX. 5



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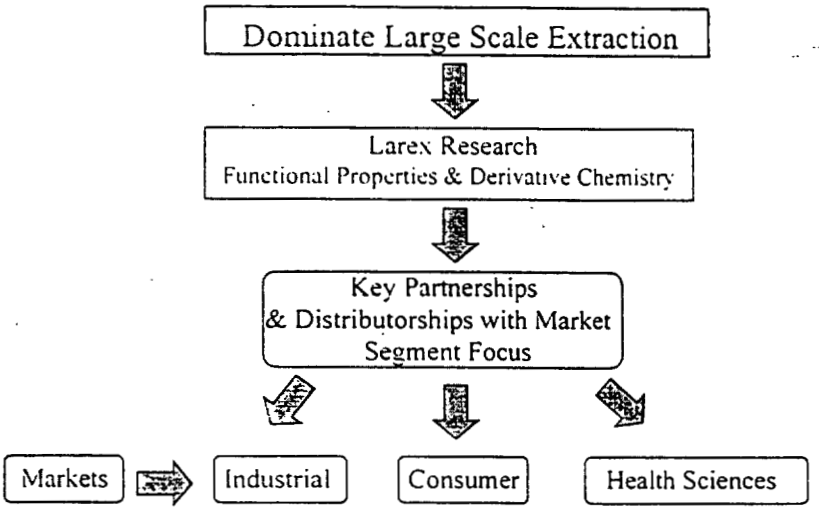
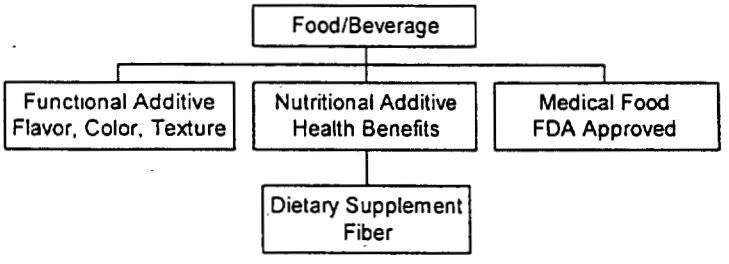
LAREX FOCUS & MARKET LINKAGE



LAREX. 7

Food Market Overview



LAREX. 8

Food Applications

- Moisture Retention
  - Baked Goods (Breads, Tortilla's)
- Dietary Fiber Source
  - Cakes, breads, snack bars
  - Beverages
- Glazing, Coating
  - Shiny, slightly brittle coating
- Flavor Encapsulation

LAREX. 9

Current Product Offering

- LaraPrint, Larex Dispersant-Printing/Industrial
- LaraCare-Personal Care
- L'Extra-Food/Beverage (Flavor, texture)
- FIBERAID - Dietary Fiber
- Larex AC-9 - Animal Feed
- Cellsep-Biomedical

LAREX. 10

Arabinogalactan

Trade Name Correlations

St. Regis Paper Company	LAREX
Stractan 10	LSC-1
Stractan 15	LSC-1
Stractan 2	L'Extra 2,000

LAREX Food Product Specific Processing Steps

LSC-1	F100	F2000	FIBERAID
Extraction	Extraction	Extraction	Extraction
⇓	⇓	⇓	⇓
Screening	Preservative Additive	Decolorizing	Decolorizing
⇓	⇓	⇓	⇓
Separation	Spray Drying	Carbon Filtering	Carbon Filtering
⇓		⇓	⇓
Evaporation		Spray Agglomeration	Ion Exchange
⇓			⇓
Preservative Additive			Spray Agglomeration

7701

Certificate of Achievement

Manhattan Kansas

AMERICAN INSTITUTE OF BAKING
FOUNDED 1919

Larex, Inc.

Cohasset, Minnesota

was inspected by a qualified Food Safety Auditor of the AIB on

November 17, 1997

and at that time, was found to have fulfilled the requirements of the Department of Food Safety/Hygiene.

EXCELLENT

President

Vice President

Chairman of the Board

Vice President Audit Services

000071

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Certificate of Participation

Manhattan Kansas

Larex, Inc.
Cohasset, Minnesota

is active in a continuing program of improving and maintaining food safety programs. They have subscribed this year to the In-Plant Food Safety/Hygiene Audit Training Program of the Department of Food Safety/Hygiene.

1997

President

Chairman of the Board

Vice President

Director of Field Services

000072

Species of the Genus *Larix* Known to Contain Significant Quantities

Species	Common Name
Larix:	
occidentalis	**Western Larch**
decidua	**European Larch**
laricina	**Tamarack**
lyallii	**Alpine Larch**
leptolepis	**--**
korean	**Korean Larch**
dahurica	**Mongolian Larch**

Arabinogalactan Physical Properties from Various Larch Species

Species	Yield (% of wood)	Gal/Ara	$[\alpha]_D$ degrees *
L. dahurica (gmelini) Mongolian larch	16-24	5.5	
L. dahurica		4.1-5.5	
L. gmelini, var. *japonica*	15.7	4.3 (B)	
L. decidua European larch		5.8	+12.2
L. decidua			+16.5
L. decidua		5.6	+20
L. decidua		5.9	
L. decidua	3.4	5.7	
L. decidua	15.9	6.9	+17.6
L. laricina Tamarack	4	5.7	+13.0
L. laricina	3.9 (A)	5.4	
L. laricina	5.6	3.8	+11
L. leptolepis Japanese Larch	3	5.9	
L. leptolepis			
L. lyallii Alpine larch	8.0 (A)	7.8	
L. lyallii	5.6 (A)	4.9	
L. lyalli	2.1 (A)	2.6	
L. occidentalis Western larch		5.4	
L. occidentalis			+12.1
L. occidentalis		5.9	
L. occidentalis		5.2	
L. occidentalis	8.4 (heartwood)	5.3	
L. occidentalis	0.9 (sapwood)	6.2	
L. potaninni	8.6	4.3 (A) 3.8 (B)	+7 +10
L. sibirica Siberian larch	7.2 (A)	7.3	
L. sukaczevii		3.6	
	5.3	5.4	

[Timell, 1965, VOL. 4 TAB 11]

COMPARISON OF LSC-1 ARABINOGALACTAN PRODUCTS FROM WESTERN LARCH AND TAMARACK

AVERAGE VALUES OF FIVE LOTS	WESTERN LARCH	TAMARACK
Refractive Index (%)	51.28	52.23
Ash (%)	0.31	0.79
Chloride (ppm)	68.0	93.3
Insoluble Matter (%)	<0.1	<0.1
Molecular Weight	20,822	19,8133
PH	4.62	4.92
Phenol (ppm)	2.03	1.17
Specific Gravity	1.22	1.22
Turbidity (NTUs)	1.45	2.31
UV 280 nm	0.8861	0.6307
Viscosity cP	292.75	199.0

Final Product Specifications for LAREX Arabinogalactan LSC-1

Food Grade	
Chemical Specifications	
Arabinogalactan	50-55%
Arsenic	<3 ppm
Total Ash	<5%
Chloride	<150 ppm
Heavy Metals as lead	<10 ppm
Insoluble Matter	<0.1%
Molecular Weight	16,000 - 25,000
pH	3.0 - 6.0
Phenol	1.0 - 3.0 ppm
UV 280 nm	0.55 - 1.20
Viscosity	<500 cps
Microbiological Specifications	
Aerobic Plate Count	<1,000 CFU
Salmonella sp.	Negative
Staphylococci sp. (coagulase positive)	<10 CFU
Eschericia coli	<10 CFU
Yeast	<100 CFU
Mold	< 100 CFU

Final Product Specifications of LAREX Decolorized Arabinogalactan

Food Grade	
Chemical Specifications	
Arabinogalactan	>90% (d.w.b.)
Arsenic	<3 ppm
Total Ash	<10%
Bulk Density	<0.75 g/ml
Chloride	<1500 ppm
Heavy Metals as lead	<10 ppm
Insoluble Matter	<0.1%
Molecular Weight	16,000 - 25,000
pH	4.0 - 8.0
Phenol	<5.0 ppm
UV 280 nm	0.5 - 2.0
Viscosity	<5.0 cps
Microbiological Specifications	
Aerobic Plate Count	<1,000 CFU
Salmonella sp.	Negative
Staphylococci sp. (coagulase positive)	<10 CFU
Eschericia Coli	<10 CFU
Yeast	<100 CFU
Mold	< 100 CFU

Heavy Metal and Mineral Analyses of Five Lots of LSC-1 Arabinogalactan From Western Larch

Sample Lot Numbe	Iodine (%)	Potassium (mg/Kg)	Calcium (mg/Kg)	Magnesium (mg/Kg)	Sodium (mg/Kg)	Aluminum (mg/Kg)	Arsenic (mg/Kg	Boron (mg/Kg	Cadmium (mg/Kg)	Chromium (mg/Kg)
0018 96 226 02	0.0006	1343	36.84	42.75	663.7	5.808	< 0.067	< 3.319	< 0.365	< 0.398
0018 97 127 01	0.0015	970.0	<6.609	42.99	498.9	5.683	<0.067	1.840	<0.363	<0.397
0018 97 133 01	0.0011	929.0	<6.628	37.48	550.0	4.574	<0.067	4.010	<0.365	<0.398
0018 97 155 01	0.0032	1074	8.567	47.09	290.2	5.338	<0.066	3.295	<0.362	0.527
0018 97 167 01	0.004	866.8	13.45	37.39	452.6	5.051	<0.066	<3.28	<0.361	<0.394

Sample Lot Numbe	Copper (mg/Kg	Heavy Metals as Lead (ppm)	Iron (mg/Kg)	Manganese (mg/Kg)	Mercury (mg/Kg)	Nickel (mg/Kg)	Silicon (mg/Kg	Sulfur (%)	Titanium (mg/Kg)	Zinc (mg/Kg)
0018 96 226 02	<0.265	<10	10.85	3.42	0.019	0.664	27.45	<0.01	<0.398	0.431
0018 97 127 01	<0.363	<10	8.657	5.49	<0.019	<0.661	65.06	0.01	<0.398	1.19
0018 97 133 01	0.497	<10	7.590	5.07	<0.02	<0.663	71.59	<0.01	<0.398	1.359
0018 97 155 01	0.297	<10	7.743	6.89	<0.02	<0.663	48.93	<0.01	<0.395	0.824
0018 97 167 01	0.558	<10	10.63	4.89	<0.019	<0.656	53.92	<0.01	<0.394	1.213

MVTL Laboratories, 1997, VOL. 2 TAB 29]

000078

MICROBIOLOGICAL PROFILE OF FIVE LOTS OF LSC-1 ARABINOGALACTAN FROM WESTERN LARCH

Lot #	Aerobic Plate Count (CFU/g)	Coliform Count (CFU/g)	Escherlcia coli (CFU/g)	Staphylocòcci , Coag pos (CFU/g)	Mold Count (per g)	Yeast Count (CFU/g)	Salmonella	Weight for Salmonella (g)
00189622602	<10	<10	<10	<10	<10	<10	Negative	86
00189712701	<10	<10	<10	<10	<10	<10	Negative	88
00189713301	<10	<10	<10	<10	<10	<10	Negative	84
00189715501	<10	<10	<10	<10	<10	<10	Negative	88
00189716701	<10	<10	<10	<10	<10	<10	Negative	88

[MVTL Laboratories, 1997, VOL. 2 TAB 29]

Microbiological Profile of Five Lots of Decolorized Arabinogalactan from Western Larch

Lot #	Aerobic Plate Count (CFU/g)	Coliform Count (CFU/g)	Eschericia coli (CFU/g)	Staphylococci Coag pos (CFU/g)	Mold Count (per g)	Yeast Count (CFU/g)	Salmonella	Weight for Salmonella (g)
002797016-01	<10	<1	<1	<10	<10	<10	Negative	100
003497065-01	<10	<1	<1	<10	<10	<10	Negative	100
003697149-01	50	<1	<1	<10	<10	<10	Negative	100
A7-170B	<10	<1	<1	<10	<10	<10	Negative	100
003897175-01	50	<1	<1	<10	<10	<10	Negative	100

History of Use Of Arabinogalactan

1922 - As a raw material for Mucic Acid

1965 - As a Food Additive for use in foods as an emulsifier, stabilizer, binding or viscosity agent for essential oils, flavors, non-nutritive sweeteners, salads dressings, and pudding mixes

Pre-1994 - As a soluble dietary fiber supplement

1962-1997 - As a preferred ingredient in food composition patents

Occurrence of Arabinogalactan in Common Foods

Source in Foods	Reference
Coffee Beans	[Fincher, et al., 1974, VOL. 6 TAB 16]
Green Coffee Beans	[Wolfram, et al., VOL. 8 TAB 16]
Roasted Coffee Beans	[DeMaria, et al., 1994, VOL. 6 TAB 14]
Soybean Seeds	[Fincher, et al., 1974, VOL. 6 TAB 16]
Rape Seed	[Fincher, et al., 1974, VOL. 6 TAB 16]
Apple Fruit	[Fincher, et al., 1974, VOL. 6 TAB 16]
Broad Bean Leaves	[Fincher, et al., 1974, VOL. 6 TAB 16]
Cultured Tomato Cells	[Fincher, et al., 1974, VOL. 6 TAB 16] [Pogson, et al., 1995, VOL. 7 TAB 10]
Wheat Flour	[Meuser, et al., 1986, VOL. 7 TAB 5] [Medcalf, et al., 1967, VOL. 7 TAB 4]
Rye Flour	[Meuser, et al., 1986, VOL. 7 TAB 5]
Maple Syrup	[Adams, 1964, VOL. 6 TAB 1]
Radish	[Kikuchi, et al., 1993, VOL. 7 TAB 2]
Black Gram	[Susheelamma, et al., 1994, VOL. 7 TAB 11]
Red Wine	[Waters, et al., 1985, VOL. 8 TAB 14]

Composition of the Fractionated Pentosan-Protein Complexes of Wheat

Fraction	Yield (g/100g flour d.m.)	Protein content (% d.m.)	Carbo-hydrate content (% d.m.)	Carbohydrate Composition (%)		
				Ara	Xyl	Gal
Arabinoxylan-protein complex	0.58	10.8	86.4	34.7	64.7	traces
Arabinogalactan-protein complex	0.14	5.2	91.2	41.0	traces	59.0

Exposure

- Man has had a long history of exposure to arabinogalactan and arabinogalactan proteins
- History of Safe Use since 1965
- FEMA GRAS Decision Based on an 85% use level in candy - 1972
- Current safe use as a soluble dietary fiber supplement
- Detailed exposure estimates by food category are not yet available

Exposure
Annual Consumption of Naturally Occurring Arabinogalactan from Wheat Flour

Arabinogalactan Protein Content of Wheat Flour (g/100g d.m.)	Carbohydrate Content (% d.m.) of Arabinogalactan Protein	Arabinogalactan Content of Wheat Flour (% d.m.)	Approximate Wheat Flour Consumption per Year (lbs.)	Approximate Daily Arabinogalactan Consumption from Wheat Flour (grams)
0.14	91.2	0.128	100 (45,400 grams)	15.88

Exposure

Effect of Doubling the Consumption of Arabinogalactan in a Normal Diet

Consumption Level Tested	Twice Daily Consumption for a 50 kg female	Twice Daily Consumption for a 60 kg male
0.8 g/kg	40.0 g	48.0 g

- Side effects minimal - sensation of fullness or wind
- Greater than twice the production of organic acids
- Significantly less ammonia generated in fecal incubates
- Lower fecal pH (6.4) than when other fiber sources were consumed
- Complete fermentation within 48 hours in fecal incubates

[Vince, et al., 1990, VOL. 11 TAB 12]

Current Uses of Arabinogalactan and Now Under Development

- Beverages
- Animal Feed and Nutrition
- Health Bars
- Bakery Items
- Soluble Dietary Fiber Supplements
- Flavor Control
- Flavor Encapsulation

Functional Aspects of Arabinogalactan Utilized in Product Development

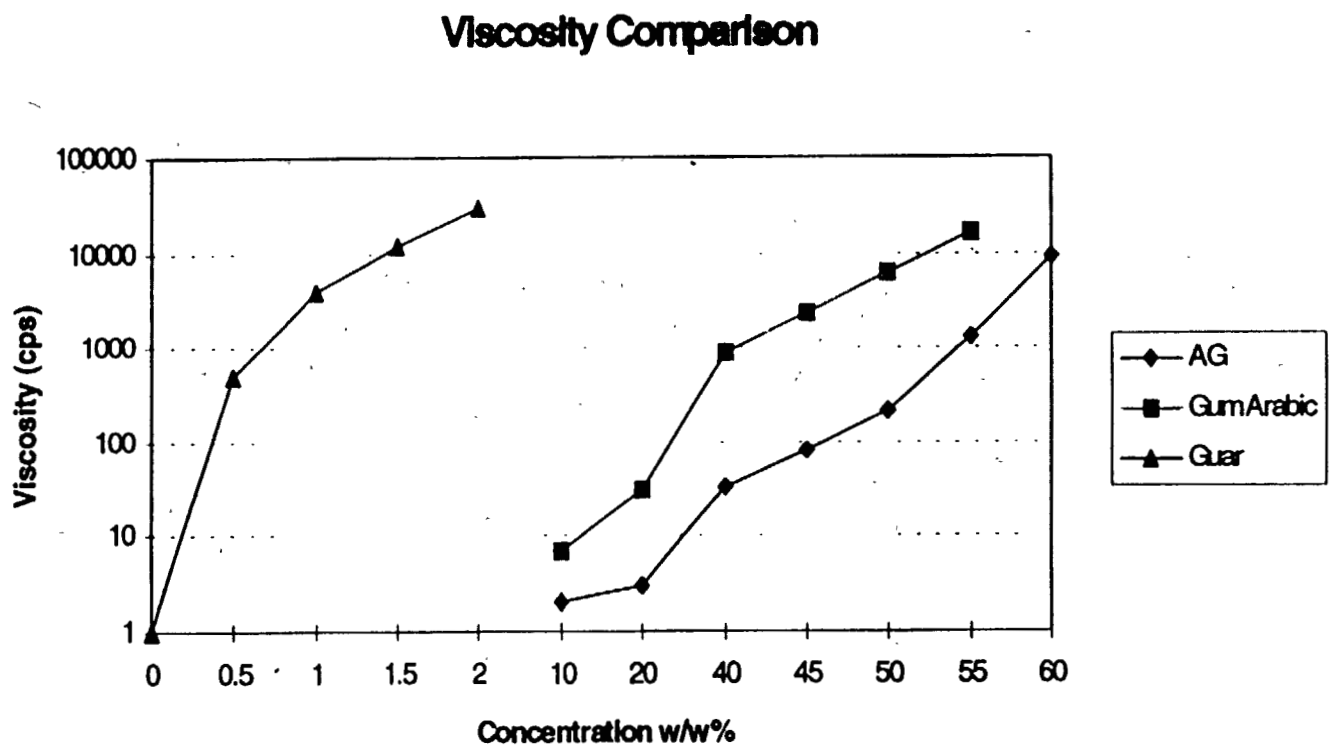
Functional Property	Use	Level Used
Soluble Fiber		
	1. To encourage growth of beneficial *Bifidobacterium*	0.1 to 5.0% of feed
	2. To provide a hypocholesteremic soluble dietary fiber	
Bulking Agent with Artificial Sweetners		
	1. To replace the bulk and viscosity of sugar	35% in Low-Calorie Maple Syrup 96% of a Sugar substitute 57% in Uncooked Fudge 86% in Butter Icing 64% in Chocolate Syrup 35% in Syrup Base
Aqueous Phase Emulsifier		
	To provide an inner aqueous phase in a w/o/w emulsion for a dressing	7% dry weight basis
Emulsifier		
	Emulsifying action for a cream/alcohol beverage	--
Thickener		
	1. To provide a hydrophilic polymer with a low viscosity for an almond nut paste for beverages and desserts.	7% dry weight basis
	2. To provide a thickening agent	1.2% in a nougat confection
	3. To provide a bulking agent with low bulk density	3-15%

Functional Property	Use	Use Level
Reduction in After-Taste		
	1. To modify the taste of artificial sweetness	< 2.5% of the final product
Film-Former		
	1. Encapsulating coating for flavors	3-6 parts by weight to the flavorant
	2. Edible Film	
	3. Film-former for browning composition	0.01-1.0% of a browning composition
Bulking Agent		
	1. To provide a partially non-digestible bulking agent for a low-calorie, low-fat chocolate confectionery	25-60%
	2. To provide a tasteless bulking agent for an adhesive sweetening mixture for nuts	--
	3. To provide a gum-type bulking agent for a "slush" partially frozen beverage	< 1%
	4. To provide bodying and bulking agent for reduced calorie candy	11-28% as a replacement for fat and sweetened condensed skim milk
Stabilizing Agent		
	1. Stabilizing Agent for aspartame in chewing gum	--
	2. To provide a stabilizer with at least 4 monosaccharide units as a preventative agent against browning	40% of a solids composition
Component of Sugar Substitutes		
	1. To provide a derivative for a novel sweetening compound	--
Gum Product		
	To provide a cultured gum substitute for gum arabic	--
Foam Adhesive		
	As a foam improver in beer containing chemical preservatives	40 ppm

Average Nutritional Values of Five Lots of a LAREX Decolorized Arabinogalactan Product

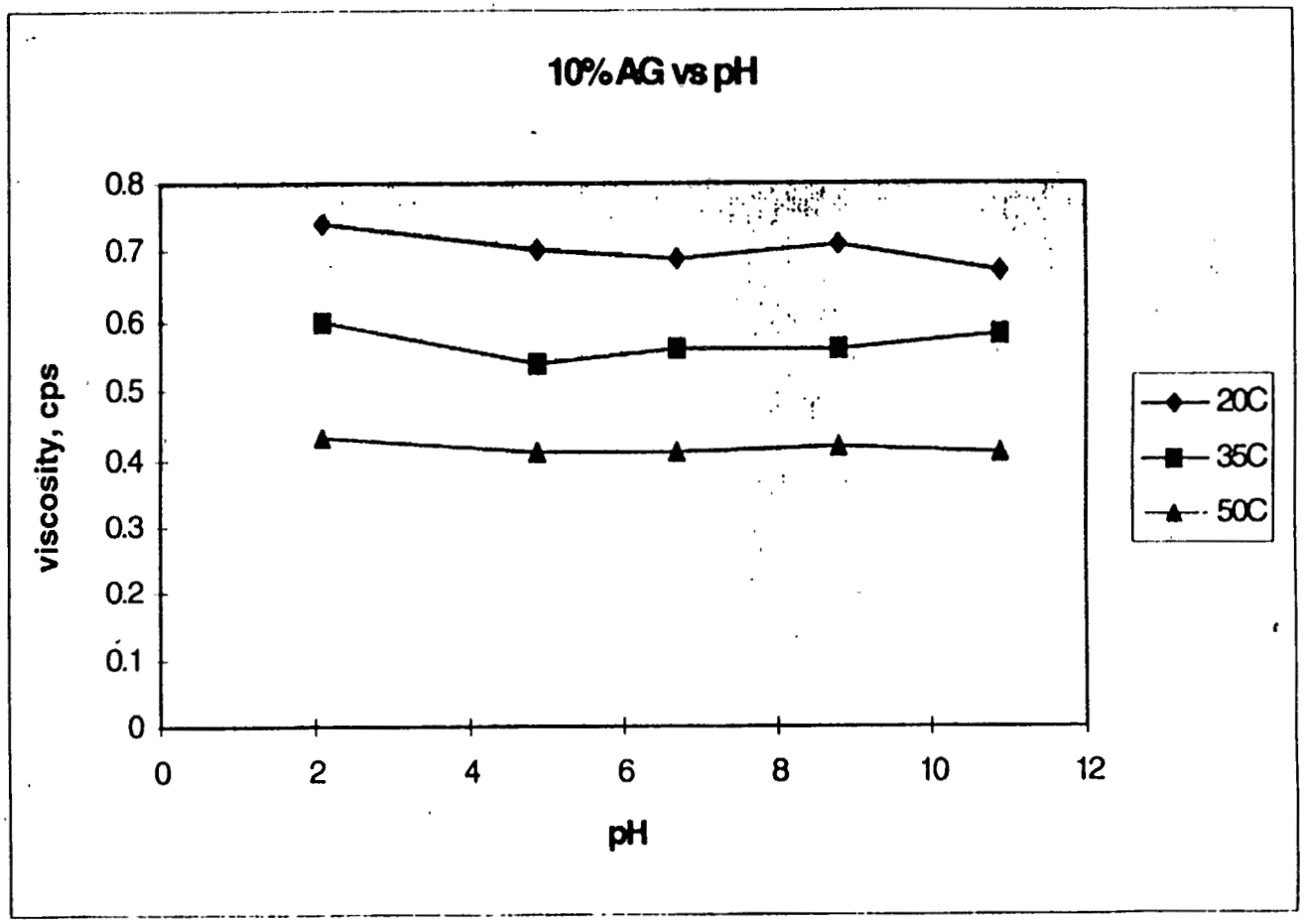
Moisture (%)	4.74
Protein (%)	0.47
Fat (A.H.) (%)	0.23
Ash (%)	5.27
Carbohydrates (%)	89.3
Total Dietary Fiber (%)	79.02
Calories (Kcal/100g)	361.22

Larex® Arabinogalactan



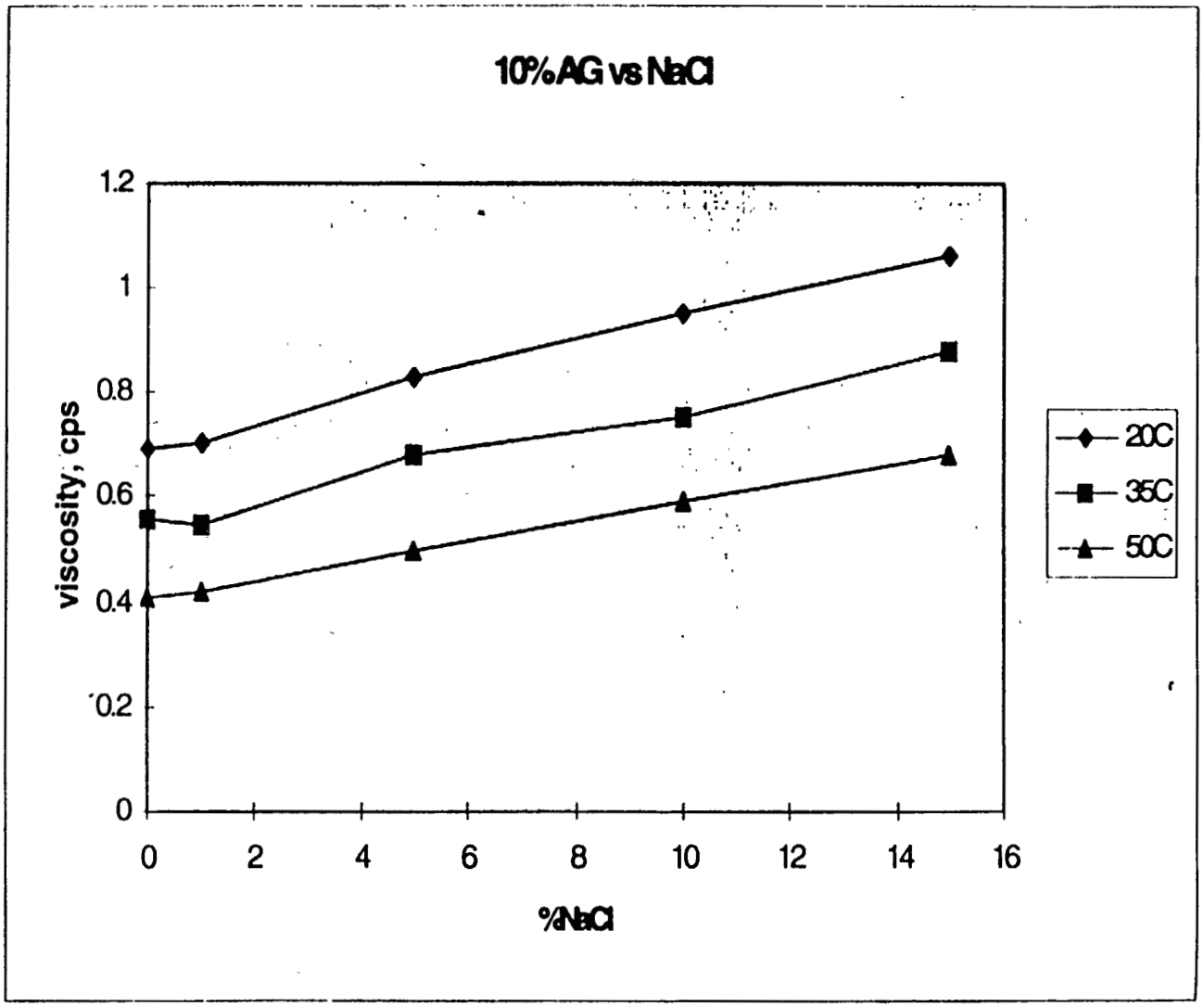
Larex® Arabinogalactan- pH Compatibility

pH	Viscosity, cps		
	20C	35C	50C
2.1	0.74	0.6	0.43
4.9	0.7	0.54	0.41
6.7	0.69	0.56	0.41
8.8	0.71	0.56	0.42
10.9	0.67	0.58	0.41



Larex® Arabinogalactan- Salt Compatibility

NaCl%	Viscosity, cps 20C	35C	50C
0	0.69	0.56	0.41
1	0.7	0.55	0.42
5	0.83	0.68	0.5
10	0.95	0.75	0.59
15	1.06	0.88	0.68



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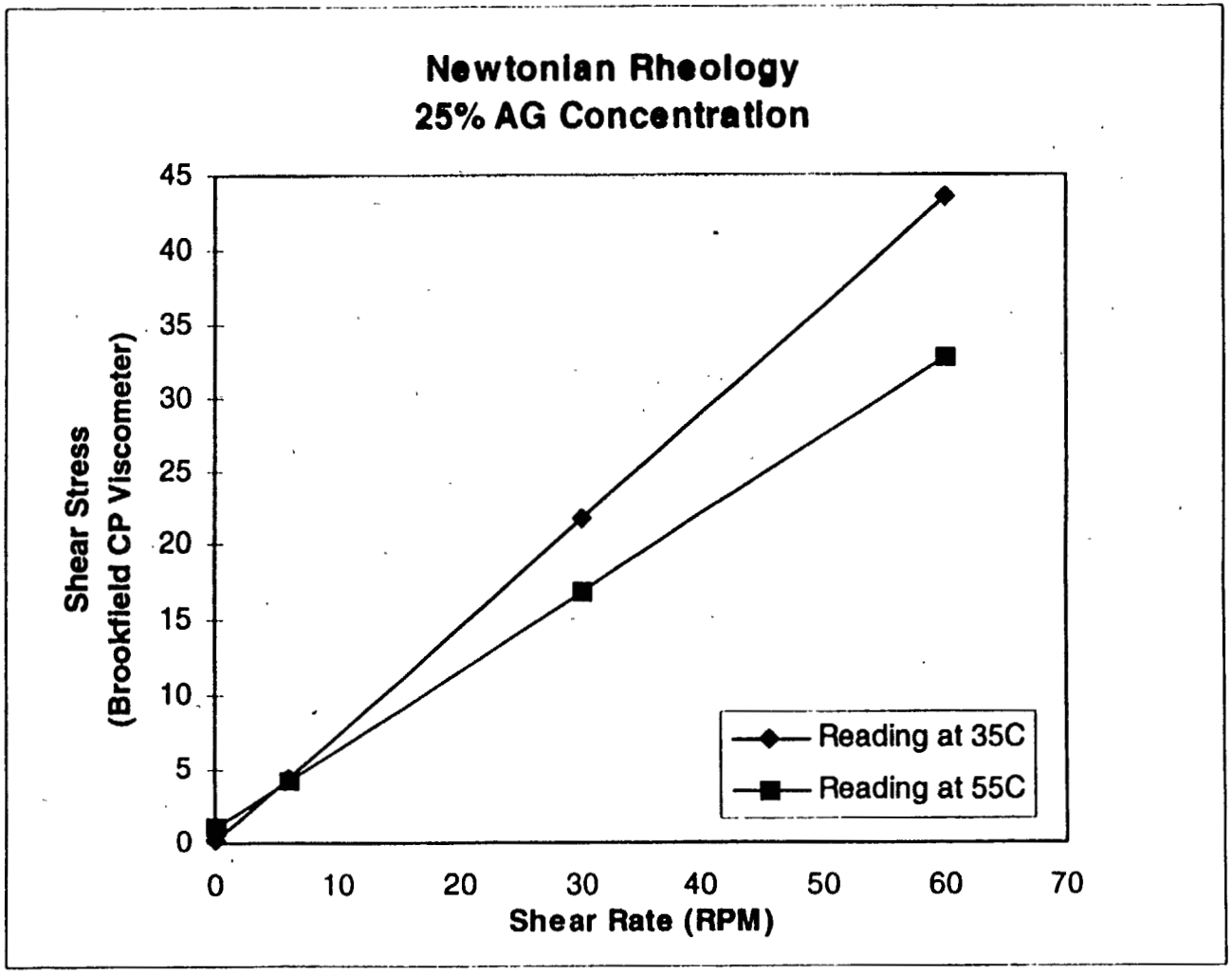
Larex® Arabinogalactan



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Larch Arabinogalactan

- AG can be added to existing systems
- AG addition to most systems will have a beneficial impact on system rheology and stability
- Unlike most natural polysaccharides, AG addition will modify system rheology without increasing system viscosity

000095

Low Mouth-Feel Impact

Concentration weight%	FIBERAID Viscosity (cps)	Benefiber Viscosity (cps)	%RDI in 10 oz
0.50	<1.0	1.03	5%
1.00	<1.0		10%
2.00	<1.0		20%
3.00	<1.0		30%
10.00	1.46		100%
30.02	5.22		300%
	Onset of FIBERAID Mouthfeel		Brookfield LVT

960000

Straight Dough White Pan Bread

Variables	Specific Volume cc/g	CrumbScan™ Fineness	Total Quality
CNT	5.41	833	76.75
0.5% AG	5.28	892	77.00
1.0% AG	5.14	878	79.00
1.5% AG	5.27	869	77.50

Crumb Firmness Values of Straight Dough White Pan Bread

	Grams Force					
Variable	Day 1	S.D.	Day 4	S.D.	Day 7	S.D.
CNT	122	5.6	238	22.0	278	14.7
0.5% AG	132	9.4	230	15.6	309	13.8
1.0% AG	136	5.5	281	16.1	318	11.0
1.5% AG	143	14.8	266	16.2	326	22.6

Objectively Measured Characteristics of Tortillas

Variables	Diameter (cm)	Stack Height/10 (cm)
CNT	20.6	3.27
1.0% AG	19.5	2.86
2.0% AG	19.5	2.74
5.0% AG	19.1	2.47

Firmness and Stretchability Values of Tortillas

Variable	Grams Force (Firmness)				Mm Dist ance Str etchabi ity)			
	Day 1	S.D.	Day 6	S.D.	Day 1	S.D.	Day 6	S.D.
CNT	987	129.4	1018	71.4	17.1	0.9	12.9	0.3
1.0% AG	947	105.1	966	134.5	16.7	1.1	12.9	1.1
2.0% AG	1012	101.9	978	93.9	16.9	0.5	12.8	0.6
5.0% AG	1035	82.7	970	52.7	17.5	0.6	11.9	0.5

Subjectively Measured Characteristics of Tortillas

Variable	Dough Score	Tortilla Score		
		External	Internal	Total Quality
CNT	14.50	23.50	40.00	78.00
1.0% AG	14.50	23.50	40.00	78.00
2.0% AG	15.00	23.50	41.00	79.50
5.0% AG	15.50	23.00	41.00	79.50

YELLOW LAYER CAKE

Variable	Additional Water %	Specific Gravity	Batter Viscosity, cps	Specific Volume	Total Quality
Series 1: CNT	0.0	0.7425	19,000	3.67	84.50
1.0% AG	0.0	0.7387	19,500	3.53	84.50
5.0% AG	0.0	0.7733	15,550	3.33	78.50
5.0% AG	2.5	0.7771	15,000	3.27	78.50
5.0% AG	5.0	0.7702	15,000	3.27	76.00
5.0% AG	15.0	0.7716	11,000	3.21	78.25
5.0% AG	20.0	0.7887	9,000	3.17	77.50
10.0% AG	5.0	0.7589	17,500	3.17	75.25
10.0% AG	15.0	0.7449	17,000	3.31	78.50
Series 2:					
CNT	0.0	0.7562	17,000	3.65	83.50
5.0% AG	0.0	0.7616	16,500	3.49	81.50
5.0% AG	20.0	0.7979	8,500	3.18	76.25
10.0% AG	0.0	0.7884	14,500	3.14	69.50
10.0% AG	40.0	0.8360	4,000	2.89	69.00

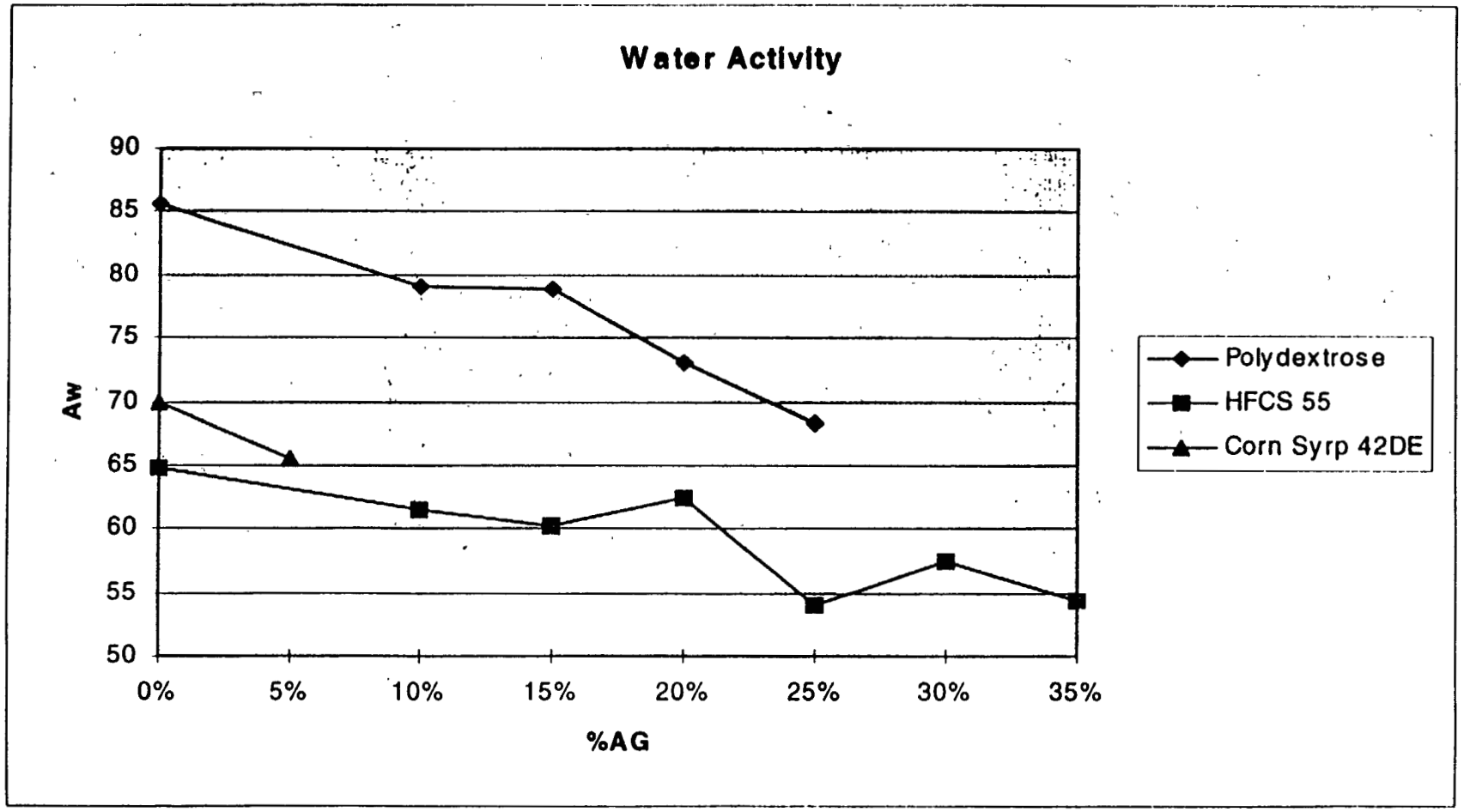
Sugar Snap Cookies

Variables	Diameter (mm)	Height (mm)	Spread/Height Ratio	Total Score
CNT	398	46	8.65	91.0
1.0% AG	407	44	9.25	89.5
2.0% AG	417	42	99.2	88.5
5.0% AG	419	41	10.22	82.5

Subjective Measurements of Sugar Snap Cookies Shelf-Life Study - Seven Days After Baking

Variable	Dough Characteristics	Cookie Score		
		External	Internal	Total Score
CNT	Standard	37.0	27.0	91.0
1.0% AG	Standard	35.5	27.0	89.5
2.0% AG	Standard	34.5	27.0	88.5
5% AG	Slightly Soft	32.0	24.5	82.5

L'Extra Water Activity



Binder for Sugar Coating

Tablets containing 1.5% AG vs. no binder

- Better impact resistance

Tablets containing AG vs. gelatin and acacia

- Less Yellowing
- Faster Disintegration
- Better Edge Filling and Less Cracking

000102

Effectiveness for Tablet Hardness Improvement

Formula	Hardness at Maximum Tableting Pressure (kg±SD, n=5)
Blank Tablet	5.8 ± .06
Arabinogalactan Additive Tablet (5%)	11.4 ± 0.5

Effectiveness for Tablet Disintegration

Formula	Disintegration Time (min ± SD, n=12)	Tablet Hardness (Kg ± SD, n=10)
Blank tablet	7.3 ± 0.6	4.7 ± 0.3
Arabinogalactan additive tablet (5%)	2.9 ± 0.2	5.3 ± 0.4

Effectiveness for Granulation

Formula	Disintegration Time (min ± SD, n=12)	Degree of Abrasiveness (% ± SD, n=10)
Blank Tablet	60 <	0.76 ± 0.16
Arabinogalactan additive (5%)	6.4 ± 0.9	0.50 ± 0.07
Arabinogalactan additive tablet (10%)	2.0 ± 0.0	0.50 ± 0.03

Food Additive Petition

- Stein, Hall and Company and St. Regis Paper Company submitted a Food Additive Petition to FDA which was filed in 1964
- Broad use of Arabinogalactan was not envisioned at the time
- Approval was given for use in foods as an emulsifier, stabilizer, binding or viscosity agent for essential oils, flavors, non-nutritive sweeteners, salad dressings, and pudding mixes
- The petition contained:
  - a brief review of the process
  - a chemical description of the substance
  - Safety studies using three species of test animals
  - feeding studies with high levels of arabinogalactan incorporation (up to 25%) of the ration

Test Animal Safety and Feeding Studies

Test Animal	Type of Test	Exposure	Duration	Comment
Rats	Acute Toxicity	12.9 k/Kg	--	LD_{50}
Rats	Feeding Study	0-20% of diet	8 weeks	No Nutritional Level
Rats	30-Day Preliminary toxicity study	0-25% of diet	30 days	Slight diarrhea 25% group Innocuous to rats
Rats	Caloric Value Study	0-29% of diet	1 week	Diarrhea in High groups
Rats	Caloric Value Study	1 and 3 grams/day	1 week	Rats lost weight at the high level
Beagle Dogs	Six-month Chronic Toxicity Study	1-10% of diet	6 months	No indication of toxicity was noted
Pigs	Feeding Study	0-20% of diet	1 week	Well utilized at the 10% level
Pigs	Metabolism Trial	0-30% of diet	5 day adjustment period 4 day collection period	Well utilized

63-DAY
PIG FEEDING STUDY

DIETARY TREATMENTS

	0% AG	10% AG	20%AG
Av. Daily Feed Consumption (lbs)	5.50	5.60	6.20
Av. Daily Gain (lbs)	1.79	1.85	1.83
Feed Efficiency (lbs Feed/lb gain)	3.09	3.03	3.38
NEg for ratio (kcal/g DM)	1.760	1.755	1.451
Neg of AG (kcal/g DM)	-	1.713	0.392
Neg Intake (Kcal/day)	3847.7	3965.8	3713.0

PIG METABOLIC STUDY
FOUR DAY COLLECTION PERIODS

DIETARY TREATMENTS

	0%	10%	20%	30%
DM Digestibility (%)	89.4	88.7	83.4	77.6
DM Digestibility of AG (%)	-	83.7	54.7	57.2
Digestible Energy (kcal/g)	3.873	3.810	3.502	3.425

Arabinogalactan Fermentation by Human Fecal Bacteria

Several Authors Showed That:

AG was fermented by indigenous colonic bacteria

[Mazur, et al., 1993, VOL. 11 TAB 7, Englyst, et al., 1987, VOL. 10 TAB 9, Salyers, et al., 1981, VOL. 11 TAB 10, Macfarlane, et al., 1995, VOL. 11 TAB 6, Vince, et al., 1990, VOL. 11 TAB 12]

Branched chains of AG fermented along with the backbone

[Englyst, et al., 1987, VOL. 10 TAB 9, Salyers, et al., 1981. VOL. 11 TAB 10, Mazur, et al., 1993, VOL. 11 TAB 7, Macfarlane, et al., 1995, VOL. 11 TAB 6]

AG was able to induce the enzymes necessary for its degradation

[Englyst, et al., 1987, VOL. 10 TAB 9, , Salyers, et al., 1981. VOL. 11 TAB 10]

AG was shown to reduce the level of ammonia in the colon

[Vince, et al., 1990, VOL. 11 TAB 12]

AG was shown to be slowly fermented to short chain fatty acids

[Englyst, et al., 1987, VOL. 10 TAB 9, Vince, et al., 1990, VOL. 11 TAB 12]

ASSAY FOR MUTAGENICITY

RESULTS OF A *SALMONELLA/* MICROSOME ASSAY SHOWED THAT ARABINOGALACTAN WAS NOT MUTAGENIC AT DOSE LEVELS RANGING FROM 156-5,000 µg/plate.

ARABINOGALACTAN AND INSULIN RESPONSE

50 grams of arabinogalactan and 0.11 grams of sodium saccharin were shown not to influence insulin response

Neutral Red Uptake Assay (NRU_{50})

	NRU_{50} (µg/ml)	Description
Arabinogalactan	3650	Very Mild
Sodium Lauri Sulfate	4	Harsh
Body Shampoo	50	Slightly Irritating
Baby Lotion	700	Mild
Mild Detergent	3000	Very Mild

[Harbell, et al., 1996, VOL. 11 TAB 1]

Arabinogalactan Manufactured Using the Larex Process in Accordance with Current Good Manufacturing Practice for Use in Food

Larex, Incorporated (Larex) convened a panel of scientific experts (Panel), qualified by training and experience in the areas of toxicology, nutrition, carbohydrate chemistry, biochemistry, microbiology, hydrocolloid applications, and regulatory compliance to render opinions on the GRAS status of arabinogalactan produced by Larex, and meeting the specifications described herein, for use in foods to achieve certain technical effects. A comprehensive search of the scientific literature was conducted by Lee Dexter and was made available to the Panel in the form of a twelve (12) volume report. The Panel independently and individually critically reviewed this material and other materials deemed appropriate.

Panel members conferred by telephone, and met with representatives of Larex in Washington D.C. on 16 January, 1998. Following presentation by these experts, and extensive discussion, the Panel went into Executive Session and prepared the following report:

Based on the data and information reviewed, the Panel provides the following statements about arabinogalactan and its proposed general use in food: The arabinogalactan derived from trees of the genus *Larix* (Larch) is a unique hemicellulosic product, in that it is easily extractable by water in a pure form from non-delignified plant tissues. Other hemicellulosic products have required chemical additives and/or mechanical treatments to extract them from their plant sources, and the literature has indicated that these extractants alter the polysaccharides to a certain degree [Whistler, et al., 1970, Stephen, 1983, and Wilkie, 1986]. Therefore, the arabinogalactan produced by LAREX can be considered equivalent to naturally occurring arabinogalactan [Whistler, et al., 1970].

Many authors have demonstrated that arabinogalactan is a common constituent of plant cell walls, and as such has had a long history of consumption by humans [Pennell, et al., 1989,]. Arabinogalactans are often complexed with protein to form a glycoprotein which has various functions in the plant cell wall [Stephen, 1983, and Schindler, et al., 1995]. Arabinogalactans have been commonly consumed by humans in such foods as maple syrup, carrots, tomatoes, soy beans, radishes, and wheat flour [Neukom, et al., 1975, Morita, et al., 1965, and Whistler, et al. 1970]. Arabinogalactan has a number of valuable properties for use in foods including moisture retention, emulsification, thickening, bulking, and the nutritional benefits of its soluble fiber content . The addition of extracted

arabinogalactan to various foods, including baked goods such as cakes, cookies and yeast raised breads, has demonstrated a self-limiting level, beyond which the quality of the product begins to decline [American Institute of Baking, 1997].

The arabinogalactans manufactured by Larex are produced in a food grade plant in Cohasset, Minnesota, which complies with all state and federal regulations regarding food production.

Following it's independent and critical review of available information, including a history of safe use, the Panel concluded that arabinogalactan manufactured using the Larex process in accordance with cGMP, and meeting the specifications described herein, is GRAS for use in foods in the minimum quantity required to produce it's intended effects, as a binder, bodying agent, dough strengthener, emulsifier, firming agent, flavor enhancer, formulation aid, humectant, lubricant and release agent, processing aid, stabilizer and thickener, and surface finishing agent.

Signatures:

Joseph F. Borzelleca, Ph.D. Date: 16 Jan 98

Darrell G. Medcalf, Ph.D. Date: 1/16/98

Ralph Moorhouse Ph.D. Date: 1/16/98

Cleve Denny B.A. Date: 1/16/98

SUBMISSION END

AM

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

MEMORANDUM

TO: RUDAINA ALREFAI, PHD. **PAGES:** 5

FROM: LEE B. DEXTER

DATE: MAY 10, 1999

RE: GRAS NOTIFICATION CLAIM FOR ARABINOGALACTAN

Please find attached the letter we discussed. I will call this afternoon to make sure that I have included all of the necessary elements.

DUPLICATE

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

March 24, 1999

Rudaina Alrefai, PhD.
Division of Product Policy, HFS-206
Office of Premarket Approval
Center for Food Safety and
Applied Nutrition
Food and Drug Administration
200 C. St. S.W.
Washington, D.C. 20204

Re: GRAS Notice (GRN) No. 000017

Dear Dr. Alrefai:

Thank you for supplying me with the pertinent pages from the *Federal Register* which outline the requirements for a claim for exemption based on a GRAS determination. This letter in conjunction with the summary already submitted, will provide the necessary information for a GRAS Notification.

In accordance with 21 CFR § 170.36, Larex, Incorporated (Larex) of St. Paul, Minnesota claims that the use of arabinogalactan in foods manufactured under current Good Manufacturing Practices is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act, because the company has determined that such use is GRAS.

The notifier of this claim is:

Larex, Incorporated
2852 Patton Road
St. Paul, Minnesota
55113
ph: 1-800- 386-5300

DUPLICATE

The following items are contained in the notification summary already submitted to the office of pre-market approval:

(ii) The common or usual name
(iii) The applicable conditions of use
(iv) The basis for the GRAS determination

The data and information that are the basis for the notifier's GRAS determination are available for the Food and Drug Administration's (FDA) review and copying during normal business hours at the address for Larex, Inc. listed above. Alternatively, Larex will, upon request, send copies of any pertinent information to specified FDA offices.

Larex has based its self-determination of GRAS on scientific procedures. A signed statement (attached) by a panel of experts qualified by scientific training and experience to evaluate the safety of substances added to food, provides evidence of consensus that there is reasonable certainty that arabinogalactan is not harmful under the intended conditions of use. This GRAS exemption claim, which has been submitted in accordance with paragraph (c)(1) of 21 CFR § 170.36, will be available for public viewing during normal business hours at the offices of Larex, Inc., 2852 Patton Road, St. Paul, Minnesota 55113.

If you have any further questions concerning either this letter or the GRAS notification summary, please contact me at (512) 276-7408 or by facsimile at (512) 276-7489. Thank you very much for your consideration of GRAS Notice 000017.

Sincerely,

Lee B. Dexter /
Technical Consultant

Attachment: signed expert panel letter

Cc: Richard D. Lamb, Larex, Inc.

DUPLICATE

Arabinogalactan Manufactured Using the Larex Process in Accordance with Current Good Manufacturing Practice for Use in Food

Larex, Incorporated (Larex) convened a panel of scientific experts (Panel), qualified by training and experience in the areas of toxicology, nutrition, carbohydrate chemistry, biochemistry, microbiology, hydrocolloid applications, and regulatory compliance to render opinions on the GRAS status of arabinogalactan produced by Larex, and meeting the specifications described herein, for use in foods to achieve certain technical effects. A comprehensive search of the scientific literature was conducted by Lee Dexter and was made available to the Panel in the form of a twelve (12) volume report. The Panel independently and individually critically reviewed this material and other materials deemed appropriate.

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DUPLICATE

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Signatures:

Joseph F. Borzelleca, Ph.D. Date: 16 Jan 98

Darrell G. Medcalf, Ph.D. Date: 1/16/98

Ralph Moorhouse Ph.D. Date: 1/16/98

Cleve Denny B.A. Date: 1/16/98

AM

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

MEMORANDUM

TO: DR. RUDAINA ALREFAI

FROM: LEE B. DEXTER

DATE: MAY 12, 1999

RE: ARRIVAL OF LETTER

Dear Dr. Alrefai:

I have just checked with FedEx, and I wanted to confirm for you that the letter claiming exemption from premarket notification on behalf of arabinogalactan was received today at 200 C St. The airbill is attached below. According to the representative, it was received by a D. Radden in the mail room.

000126

FedEx USA Airbill 812285727153

1 From: Date 5-11-99 Sender's FedEx Account Number
Sender's Name Lee B. Dexter Phone
Company Dexter & Associates
Address 15704 Webberville Rd
City Austin State TX ZIP 78724

2 Your Internal Billing Reference

3 To Recipient's Name Rudaina Alrefai, PhD. Phone (202) 418-3034
Division of Product Policy HFS-206
Company Food and Drug Administration
Address 200 C, St. S.W.
We cannot deliver to P.O. boxes or P.O. ZIP codes.
Dept./Floor/Suite/Room
Washington, State DC ZIP 20204

Sender's Copy

4a Express Package Service — Packages up to 150 lbs.
☐ FedEx Priority Overnight ☒ FedEx Standard Overnight ☐ FedEx First Overnight
☐ FedEx 2Day ☐ FedEx Express Saver

4b Express Freight Service — Packages over 150 lbs.
☐ FedEx 1Day Freight ☐ FedEx 2Day Freight ☐ FedEx 3Day Freight

5 Packaging
☒ FedEx Letter ☐ FedEx Pak ☐ Other Pkg.

6 Special Handling
☐ Saturday Delivery ☐ Sunday Delivery ☐ HOLD Weekday at FedEx Location ☐ HOLD Saturday at FedEx Location
Does this shipment contain dangerous goods?
☐ No ☐ Yes ☐ Yes ☐ Dry Ice ☐ Cargo Aircraft Only

7 Payment Bill to:
☐ Sender ☐ Recipient ☐ Third Party ☐ Credit Card ☒ Cash/Check

Total Packages Total Weight Total Declared Value $ .00

8 Rl

Questions? Call 1-800-Go-FedEx (800-463-3339)
Visit our Web site at www.fedex.com

By using this Airbill you agree to the service conditions on the back of this Airbill and in our current Service Guide, including terms that limit our liability.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

360

RETAIN THIS COPY FOR YOUR RECORDS

10:37
D. RADDEN

Lee B. Dexter & Assoc.

Technology Consultants

15704 Webberville Road
Austin, Texas 78724 USA

Telephone (512) 276-7408
Fax (512) 276-7489

TO: **Dr. Rudaina Alrefai, CFSAN**
Via Fax: (202) 418-3131

From: Lee B. Dexter

Pages: 9

Date: December 10, 1999

Re: **Exposure Section for Larex, Inc. Arabinogalactan**

Dear Dr. Alrefai:

I apologize that I have been on the road so much, for companies that were trying to finish travel before the holidays started at Thanksgiving. I have failed to maintain the information "flow" that I would have liked. Please accept my apologies for the inconvenience.

1999 DEC 15 A 9:41

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

November 6,1999

Dr. Rudaina Alrefai
Office of Premarket Approval
Center for Food, Safety and Nutrition
Food and Drug Administration
200 C St. SW HFS 206
Washington, DC 20204

Dear Dr. Alrefai:

As a result of guidance received from various CFSAN personnel, Larex, Inc. would like to submit an amendment of its notice of a claim for premarket exemption based on a GRAS determination under proposed §170.36 (GRAS Notification). This amendment contains additional information regarding the expected exposure to arabinogalactan, a soluble fiber derived from the larch tree (*Larix occidentalis).* This amendment has been prepared in accordance with the agency's guidance document "*Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet*". Triplicate copies of this document are being submitted to CFSAN at the address above. Larex would appreciate notice of the receipt of this amendment, and looks forward to any comments the agency would care to make on the material.

Calculations for the maximum exposure levels for arabinogalactan were based on the major food categories reported in USDA's *Continuing Survey of Food Intake by Individuals* for 1994-96. This information was modified to include a separate category for the use of arabinogalactan as a dietary supplement [Enns, *et al.,* 1997].

Maximum use levels were taken as those, which have been commercialized or developed as food application models for processed foods. The calculations obtained by multiplying the current good manufacturing practice maximum percentage of use by the mean intake for each food category were refined using several mitigating factors.

Larex, Inc. submits that the 90th percentile intake for arabinogalactan will fall between 3.68 and 7.36 grams per day. These consumption levels have been shown to be safely tolerated in several recent human and animal studies.

Please don't hesitate to call at the numbers listed above if your require further clarification.

Sincerely,

Lee B. Dexter
Technical Consultant

C: Richard Lamb, Director of Technical Processes, Larex, Inc.

Exposure to Arabinogalactan

The agency's guidance document "*Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet*" was used to estimate the maximum possible exposure to the arabinogalactan produced by Larex, Inc. In order to calculate the 90th percentile of consumption, mean intake levels for male and female adults over age 20 were averaged from USDA's *Continuing Survey of Food Intake by Individuals* for 1994-96. This information was modified to include a separate category for the use of arabinogalactan as a source of soluble prebiotic fiber in dietary supplement form [Enns, *et al.,* 1997 and Causey, *et al.*, 1999].

Table 1 below shows the mean intake for selected major food categories for adults. The current maximum good manufacturing use level for arabinogalactan is also shown in Table 2 for the forty-three food categories listed at 21 CFR § 170.3 (n). The correlation between the major food categories derived from the USDA food survey, and those listed at § 170.3 (n) is shown in Table 3.

The sum of the grams of arabinogalactan calculated from the mean intakes for each major food category listed on Table 1 is 208.9 grams per day. The agency's guidance document indicates that an estimate of the 90th percentile level of intake can be calculated by doubling the total mean intake. This value is 417.8 grams per day.

Companies are also advised that they may refine the values obtained by calculation, since these values are based on certain very conservative assumptions. These assumptions include:

1. That arabinogalactan would be incorporated into every food in a category

2. That arabinogalactan would always be present at the maximum level

3. That all categories containing arabinogalactan would be consumed simultaneously.

Several factors make the very high consumption levels obtained by calculation unreasonable:

1. Individuals consuming arabinogalactan at the 90th percentile shown above would be consuming approximately 28% of their diet as arabinogalactan.

2. Arabinogalactan is self-limiting in certain food formulations, especially

most baked goods.

3. Larex, Inc. is the world's only producer of arabinogalactan. The company's annual plant capacity is currently eight (8) million pounds.

4. Much of the calculated intake (>30%) is contributed by non-alcoholic beverages, a category that includes carbonated drinks. While arabinogalactan can be used at the 25% level in some beverages, it is unlikely that the ingredient will be appropriate for all beverages at that level. Solutions of arabinogalactan have very low viscosity even at very high concentrations. Arabinogalactan is often used to decrease viscosity in many applications. This property may not be desirable in all drink formulations, especially those formulated to provide a certain texture or mouthfeel.

5. Larex, Inc. arabinogalactan is a very expensive food ingredient, costing several dollars per pound. Therefore, those applications in which it will be cost effective will need to be carefully chosen, and will most likely dictate that arabinogalactan will be used at the minimum level necessary to produce a given technical or nutritional effect.

Larex, Inc.submits that a 10% rule would be more reasonable for calculating the 90th percentile. That is that 10% of the population would consume 100% of the available arabinogalactan. Currently, the 8 million pounds that could potentially be produced in the Larex facility could be divided by 10% of the U.S. population, or 27,000,000 people. In that event, the average consumption would equal 0.37 grams per day, making the 90th percentile intake 0.74 grams per day. If manufacturing capacity for arabinogalactan grew by a factor of 10 X to 80, 000,000 pounds over the next several years, then the average consumption would equal 3.68 grams, or 7.36 grams per person per day. Given the limiting factors cited above, Larex, Inc. believes that these values provide a more reasonable view of possible consumption patterns.

Table 1
Current Good Manufacturing Use Levels For Larex Arabinogalactan in Foods*

Food Category[1]	Mean Intake per Adult Over 20 (average of males and females in grams)[1]	Use Level[2] (maximum for each category)	Arabinogalactan Maximum Intake per Major Category (grams)
Total Grain Products	308	10%	30.8
Dietary Supplement; Source of Soluble Fiber[3]	1.5-4.5	100%	4.5
Vegetables and Vegetable Dishes	215.5	5%	10.7
Fruits and Fruit Preparations	164	25%	41
Milk Desserts/Cheese Products	45.5	25%	11.4
Meat, Poultry and Fish	441.	5%	22.1
Total Fats and Oils	17	7%	1.2
Legumes and Legume Dishes	25	5%	1.25
Sugars and Sweets	21.5	96%	20.6
Nuts and Seeds	3.5	7%	0.25
Total Non-Alcoholic Beverages (excluding coffee and fruit juices)	254.5	25%	63.6
Total Maximum Intake	**1,500**		**208.9**

*Based on current and proposed good manufacturing use levels of arabinogalactan.

1. Major food categories are based on those used in USDA's *Continuing Survey of Food Intake by Individuals* with use as a dietary supplement shown as a separate category [Enns, *et al.*, 1997].
2. Maximum use levels are those which have been commercialized or developed as food application models for processed foods].
3. Dietary supplement recommended intakes have been derived from human studies [Kim, et al., 1999].

Table 2
Maximum Use of Larex Arabinogalactan*
In the Food Categories Listed by the US FDA
At 21 CFR §170.3 (n)

	Food Categories	Maximum Percentage of Use
01	Baked Goods, Baking Mixes	10%
02	Beverages alcoholic	
03	Beverages and beverage bases, non-alcoholic	25%
04	Breakfast Cereals	10%
05	Cheeses	5%
06	Chewing Gum	2%
07	Coffee and tea	
08	Condiments and relishes	5%
09	Confections and frostings	85%
10	Dairy product analogs	2%
11	Egg Products	
12	Fats and oils	7%
13	Fish Products	5%
14	Fresh eggs	
15	Fresh fish	
16	Fresh fruits and fruit juices	25%
17	Fresh Meats	
18	Fresh poultry	
19	Fresh vegetables	
20	Frozen dairy desserts and mixes	10%
21	Fruit and water ices	2%
22	Gelatins, puddings and fillings	10%
23	Grain products and pastas	5%
24	Gravies and Sauces	5%
25	Hard candy	50%
26	Herbs, seeds, spices, seasonings, blends	3%
27	Jams and jellies, home prepared	
28	Jams and jellies commercial	25%
29	Meat products	5%
30	Milk, whole and skim	
31	Milk products	
32	Nuts and Nut products	7%
33	Plant protein products	
34	Poultry products	5%
35	Processed fruits and fruit juices	25%
36	Processed vegetables and vegetable juices	5%
37	Snack foods	10%
38	Soft Candy	50%
39	Soups, home prepared	
40	Soups and soup mixes	
41	Sugar, white granulated	
42	Sugar substitutes	96%
43	Sweet Sauces, toppings, and syrups	35%

*Based on Table 2 and parts F. and G. in Section II, Functionality of Larex, Inc.'s Notification document.

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

TO: **Dr. Rudaina Alrefai, CFSAN**
Via Fax: (202) 418-3131

From: Lee B. Dexter

Pages: 5

Date: December 10, 1999

Re: **Administrative Amendment for Larex, Inc. Arabinogalactan GRAS Notification**

Dear Dr. Alrefai:

Please find attached the administrative amendment for Larex, Inc. I believe that I have captured the changes that Drs. Kahl and Gaynor discussed with me.

Again, I apologize that I have failed to maintain the information "flow" that I would have liked. Please accept my apologies for the inconvenience.

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

TO: **Dr. Rudaina Alrefai, CFSAN**
Via Fax: (202) 418-3131

From: Lee B. Dexter

Pages: 10

Date: December 10, 1999

Re: **Administrative Amendment for Larex, Inc. Arabinogalactan GRAS Notification**

1999 DEC 16 A 11:39

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Again, I apologize that I have failed to maintain the information "flow" that I would have liked. Please accept my apologies for the inconvenience.

Dr. Alrefai:

My assistant has discovered that not all of the pages in this amendment were successfully faxed to you. We are re-faxing this document, and I will also e-mail it to you.

Blank Page Inserted for Pagination

Computer Technology Services, Inc.

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
AUSTIN, TEXAS 78724 USA

TELEPHONE (512) 276-7408
FAX (512) 276-7489

November 6,1999

Dr. Rudaina Alrefai
Office of Premarket Approval
Center for Food, Safety and Nutrition
Food and Drug Administration
200 C St. SW HFS 206
Washington, DC 20204

Dear Dr. Alrefai:

Larex GRAS Notification for Arabinogalactan
GRN No. 000017

This letter will clarify and amend certain points in the GRAS Notification for arabinogalactan (GRN 000017), received by the Center for Food Safety and Applied Nutrition (CFSAN) on March 11, 1999. In a telephone conversation administrators from the Center made several requests for clarification, which are covered in this letter. The points to be clarified or expanded include:

1. A declaration that the sole source material for arabinogalactan will be Western larch (*Larix occidentalis)*
2. A specification for lead as lead
3. A detailed calculation of the maximum exposure level for Larex, Inc. arabinogalactan, according to the agency's guidance document entitled *Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet"*
4. A statement that arabinogalactan is not intended for use in alcoholic beverages
5. An explanation of the specifications which apply to each arabinogalactan product.

Larex, Inc. wishes to amend the Chemical Identity section (Section I, Part F) of its Notification to indicate that the Food Grade Raw Material for arabinogalactan is limited to Western larch (*Larix occidentalis)*. Use of other species of the genus *Larix* as raw material will be covered under a separate GRAS Notification.

000161

Larex has developed a specification for lead separate from that developed for lead as heavy metals. Analysis of 5 lots of the LSC-1 arabinogalactan product derived from Western larch showed a mean level of 0.208 ppm. Analysis of 2 lots of decolorized arabinogalactan showed a mean level of 0.417 ppm lead. Based on these results, Larex, Inc. is revising its lead specifications from <10 ppm lead as heavy metals to < 1.0 ppm lead. Table 1 (below) shows the raw data, which supports this change.

Table 1
Raw Data for Lead Analyses

Decolorized Arabinogalactan Lot No. From Western Larch	Results (mg/Kg)
0034-97065-01	0.525
0036-97149-01	0.309
Mean	**0.417**
LSC-1 Arabinogalactan Lot No. From Western Larch	
00189712701	<0.211
00189713301	0.333
00189715501	<0.212
00189716701	<0.188
00189716901	<0.21
Mean	**0.231**

A detailed calculation of exposure to arabinogalactan has been submitted under separate cover. Based on a refinement of the calculations derived from the agency's guidance document, Larex, Inc. estimates that the 90th percentile intake of arabinogalactan may range from 3.68 to 7.36 grams per day, depending on growth of manufacturing capacity and market penetration.

Larex, Inc. does not intend that its arabinogalactan products will be marketed into alcoholic beverages, even though the use of the film-forming properties of arabinogalactan have been demonstrated for that industry. Therefore, Larex, Inc. wishes to revise Table 2: *Functional Aspects of Arabinogalactan Utilized in Product Development* (pages 26 and 27 of its Notification document), to delete examples of the use of arabinogalactan in alcoholic beverages. A revised Table 2 is attached to this letter.

A set of specifications for the arabinogalactan products produced by the Larex, Inc. process is provided below. These specifications were reviewed by the Expert Scientific Panel charged with reviewing the GRAS Report compiled by Larex, Inc.

The specifications are divided into two types, depending upon whether or not the end product has been decolorized. Products of the LSC-1 type have not been decolorized. Tables 3 and 4 (attached) show the specification under which each product falls.

Larex, Inc. appreciates the guidance it has received from CFSAN on this Notification. The information in this amendment is provided as a clarification to GRAS Notification No. 000017. These changes have been incorporated into the original Notification document, and a revised document will be sent under separate cover. If additional information is required, please don't hesitate to contact me at the numbers shown above. Again, we would like to thank the agency for its review of the information supporting the safe use of arabinogalactan.

Sincerely,

Lee B. Dexter
Technical Consultant

C: Richard Lamb, Larex, Inc. Director of Technical Processes

Table 2:
Functional Aspects of Arabinogalactan Utilized In Product Development

Functional Aspect	Level Used	Reference
Bulking Agent with Artificial Sweeteners		
1. To replace the bulk and viscosity of sugar	35% in Low-Calorie Maple Syrup 96% of a Sugar substitute 57% in Uncooked Fudge 85% in Butter Icing 64% in Chocolate Syrup 35% in Syrup Base	U.S. Patent No. 3,294,544 VOL. 7 TAB 20
Aqueous Phase Emulsifier		
To provide an inner aqueous phase in a w/o/w emulsion for a dressing	7% dry weight basis	U.S. Patent No. 4,632,840 VOL. 8 TAB 2
Emulsifier		
Emulsifying action for a cream/alcohol beverage	--	U.S. Patent No. 4,419,378 VOL. 7 TAB 25
Thickener		
1. To provide a hydrophilic polymer with a low viscosity for an almond nut paste for beverages and desserts	7 % dry weight basis	U.S. Patent No. 4,639,374 VOL. 8 TAB 3
2. To provide a thickening agent	1.2% in a nougat confection	U.S. Patent No. 4,714,620 VOL. 8 TAB 4
3. To provide a bulking agent with low bulk density	3-15%	U.S. Patent No. 3,704,138 VOL. 7 TAB 22

Table 2 (Continued)

Reduction in After-Taste		
To modify the taste of artificial sweetness	< 2.5% of the final product	U.S. Patent No. 4,228,198 VOL. 7 TAB 24
Film-Former		
1. Encapsulating coating for flavors	3-6 parts by weight to the flavorant	U.S. Patent No. 3,264,114 VOL. 7 TAB 19
2. Edible Film	10-20% of an aqueous solution which is dried to < 25% moisture	U.S. Patent No. 5,089,307 VOL. 8 TAB 9
3. Film-former for browning composition		U.S. Patent No. 5,139,800 VOL. 8 TAB 12
Bulking Agent		
1. To provide a partially non-digestible bulking agent for a low-calorie, low-fat chocolate confectionery	25-60%	U.S. Patent No. 4,810,516 VOL. 8 TAB 5
2. To provide a tasteless bulking agent for an adhesive sweetening mixture for nuts	--	U.S. Patent No. 5,194,278 VOL. 8 TAB 13
3. To provide a gum-type bulking agent for a "slush" partially frozen beverage	< 1%	U.S. Patent No. 1,331,518 VOL. 7 TAB 17
4. To provide bodying and bulking agent for reduced calorie candy	11-28% as a replacement for fat and sweetened condensed skim milk	U.S. Patent No. 3,800,045 VOL. 7 TAB 23
Stabilizing Agent		
1. Stabilizing Agent for aspartame in chewing gum	--	U.S. Patent No. 4,828,857 VOL. 8 TAB 6
2. To provide a stabilizer with at least 4 monosaccharide units as a preventative agent against browning	40% of a solids composition	U.S. Patent No. 4,547,377 VOL. 8 TAB 1
Component of Sugar Substitutes		
To provide a derivative for a novel sweetening compound	--	U.S. Patent No. 5,041,541 VOL. 8 TAB 8
Gum Product		
To provide a cultured gum substitute for gum arabic	--	U.S. Patent No. 5,133,979 VOL. 8 TAB 11

Final Product Specifications for Larex Arabinogalactan LSC-1

Food Grade	
Chemical Specifications	
Arabinogalactan	50-55%
Arsenic	<3 ppm
Total Ash	<5%
Bulk Density	<0.75 g/ml
Chloride	<150 ppm
Lead	<1.0 ppm
Insoluble Matter	<0.1%
Molecular Weight	16,000 – 25,000
pH	3.0 – 6.0
Phenol	1.0 – 3.0 ppm
UV 280 nm	0.55 – 1.20
Viscosity	<500 cps
Microbiological Specifications	
Aerobic Plate Count	<1,000 CFU
Salmonella sp.	Negative
Staphylococci sp. (coagulase positive)	< 10 CFU
Eschericia coli	<10 CFU
Yeast	<100 CFU
Mold	<100 CFU

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Final Product Specifications for Larex Decolorized Arabinogalactan

Food Grade	
Chemical Specifications	
Arabinogalactan	>90% (d.w.b.)
Arsenic	<3 ppm
Total Ash	<10%
Bulk Density	<0.75 g/ml
Chloride	<1,500 ppm
Lead	<1.0 ppm
Insoluble Matter	<0.1%
Molecular Weight	16,000 – 25,000
pH	4.0 – 8.0
Phenol	<5.0 ppm
UV 280 nm	0.5 – 2.0
Viscosity	<5.0 cps
Microbiological Specifications	
Aerobic Plate Count	<1,000 CFU
Salmonella sp.	Negative
Staphylococci sp. (coagulase positive)	< 10 CFU
Eschericia coli	<10 CFU
Yeast	<100 CFU
Mold	<100 CFU

Table 3
LAREX Arabinogalactan Products

Arabinogalactan Product Name	Market and Properties of Products	Applicable Specification
LaraPrint ™ B50	Ink additive for decreasing viscosity while maintaining color density: caramel colored 50% solution preserved with potassium sorbate.	LSC-1
LaraPrint ™ B100	Ink additive for decreasing viscosity while maintaining color density: tan colored powder	LSC-1
L'Extra™ F100	A fiber source: off-white powder, very low taste and odor, no precipitation in liquids, excellent dissolution.	LSC-1 (pre-drying)
LaraCare™ A200	Emulsion stabilizer, film and gloss former, dispersant, moisture control, rheology control: off-white powder, mild odor, highly soluble, excellent dissolution, and biodegradable.	Decolorized
L'Extra™ F2000	Moisture control: mouthfeel, encapsulation, bulking agent: off-white powder, low viscosity, very low taste and odor, some precipitation in liquids, excellent dissolution, used for moisture control.	Decolorized
FIBERAID™	A fiber source: off-white powder, very low taste and odor, no precipitation in liquids, excellent dissolution.	Decolorized

Table 4
LAREX Product Specific Processing Steps

Arabinogalactan Product Name	Processing Steps
LaraPrint ™ B50	extraction, screening, separation, evaporation, preservative addition
LaraPrint ™ B100	extraction, screening, separation, evaporation, preservative addition, spray drying
L'Extra™ F100	extraction, screening, separation, evaporation, preservative addition, spray drying
LaraCare™ A200	extraction, screening, separation, evaporation, decolorizing, ion exchange, spray drying, agglomeration
L'Extra™ F2000	extraction, screening, separation, evaporation, decolorizing, carbon filtering, spray agglomeration
FIBERAID™	extraction, separation, evaporation, decolorizing, carbon filtering, ion exchange, spray agglomeration

** TX CONFIRMATION REPORT ** AS OF DEC 14 '99 13:22 PAGE.01

LEE B DEXTER AND ASSO

	DATE	TIME	TO/FROM	MODE	MIN/SEC	PGS	CMD#	STATUS
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LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

15704 WEBBERVILLE ROAD
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TELEPHONE (512) 276-7408
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TO: DR. RUDAINA ALREFAI, CFSAN
VIA FAX: (202) 418-3131

FROM: LEE B. DEXTER

PAGES: 2

DATE: APRIL 6, 2000

RE: LETTER WITHDRAWING GRAS NOTIFICATION NUMBER 000017

Dear Dr. Alrefai:

Please find attached a letter withdrawing the GRAS Notification for arabinogalactan. Larex, Inc. would like to withdraw without prejudice, so that they can resubmit a revised document.

Please give Dr. Pauli my thanks for calling me in advance on this issue.

LEE B. DEXTER & ASSOC.
TECHNOLOGY CONSULTANTS

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AUSTIN, TEXAS 78724 USA

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April 6, 2000

Dr. Rudaina Alrefai
Office of Premarket Approval
Center for Food, Safety and Nutrition
Food and Drug Administration
200 C St. SW HFS 206
Washington, DC 20204

Dear Dr. Alrefai:

Larex GRAS Notification for Arabinogalactan
GRN No. 000017

Larex, Inc., White Bear Lake, Minnesota, hereby notifies the Center for Food Safety and Applied Nutrition (CFSAN), Office of Premarket Approval, that the company withdraws its GRAS Notification for arabinogalactan (GRN 000017) without prejudice. It is the intention of Larex Inc. to resubmit a revised notice of a claim for premarket exemption based on a GRAS determination under proposed §170.36.

The revised notification will incorporate the information contained in recent amendments to GRN 000017, as well as an estimate of exposure based on levels of use typical for the food industry. A revised set of specifications based on recent analytical data will also be incorporated in the new submission.

Larex, Inc. wishes to thank CFSAN officials for their cooperation and attention in reviewing GRN 000017. We anticipate that a revised document will be submitted within the next few weeks.

Sincerely,

Lee B. Dexter
Technical Consultant

CC: Richard Lamb, Director of Technical Processes,
Larex, Inc.