GR

ORIGINAL SUBMISSION

Original Submission

GRN 000544

ToxStrategies

Innovative solutions
Sound science

September 15, 2014

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Subject: GRAS Notification – Oat-Derived Beta-Glucan

Dear Sir:

On behalf of Tate & Lyle, ToxStrategies, Inc. (its agent) is submitting for FDA review Form 3667 and three copies of the notification as required. The enclosed document provides notice of a claim that the food ingredient described in the enclosed notification is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act because it has been determined to be generally recognized as safe (GRAS), based on scientific procedures, for addition to specified foods as a source of dietary fiber.

If you have any questions or require additional information, please do not hesitate to contact me at 630-352-0303, or dschmitt@toxstrategies.com.

Sincerely,

(b) (6)

Don Schmitt, M.P.H.
Senior Managing Scientist

RECEIVED
SEP 17 2014
OFFICE OF
FOOD ADDITIVE SAFETY

000002

Form Approved: OMB No. 0910-0342; Expiration Date: 02/29/2016
(See last page for OMB Statement)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

FDA USE ONLY

GRN NUMBER 000544	DATE OF RECEIPT
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

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Transmit completed form and attachments electronically via the Electronic Submission Gateway (see instructions), OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

PART I – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☐ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd)*: _____

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd)*: _____

PART II – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person: Ms. Lore Kolberg	Position: Director, Regulatory Affairs
Company *(if applicable)*: Tate & Lyle	
Mailing Address *(number and street)*: 5450 Prairie Stone Parkway	

City	State or Province	Zip Code/Postal Code	Country
Hoffman Estates	Illinois	60192	United States of America

Telephone Number	Fax Number	E-Mail Address
847-396-7608		Lore.Kolberg@tateand lyle.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person: Donald F. Schmitt	Position: Senior Managing Scientist
Company *(if applicable)*: ToxStrategies, Inc.	
Mailing Address *(number and street)*: 739 Thornapple Drive	

City	State or Province	Zip Code/Postal Code	Country
Naperville	Illinois	60540	United States of America

Telephone Number	Fax Number	E-Mail Address
630-352-0303		dschmitt@toxstrategies.com

PART III – GENERAL ADMINISTRATIVE INFORMATION

1. Name of Substance
Oat beta-glucan

2. Submission Format: *(Check appropriate box(es))*
- ☐ Electronic Submission Gateway
- ☒ Paper
- ☐ Electronic files on physical media with paper signature page

If applicable give number and type of physical media

3. For paper submissions only:
Number of volumes 1
Total number of pages 66

4. Does this submission incorporate any information in FDA's files by reference? *(Check one)*
☒ Yes *(Proceed to Item 5)* ☐ No *(Proceed to Item 6)*

5. The submission incorporates by reference information from a previous submission to FDA as indicated below *(Check all that apply)*
- ☒ a) GRAS Notice No. GRN 437
- ☐ b) GRAS Affirmation Petition No. GRP
- ☐ c) Food Additive Petition No. FAP
- ☐ d) Food Master File No. FMF
- ☒ e) Other or Additional *(describe or enter information as above)* GRN 207 and 344

6. Statutory basis for determination of GRAS status *(Check one)*
☒ Scientific Procedures *(21 CFR 170.30(b))* ☐ Experience based on common use in food *(21 CFR 170.30(c))*

7. Does the submission (including information that you are incorporating by reference) contain information that you view as trade secret or as confidential commercial or financial information?
- ☐ Yes *(Proceed to Item 8)*
- ☒ No *(Proceed to Part IV)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*
- ☐ Yes, see attached Designation of Confidential Information
- ☐ Yes, information is designated at the place where it occurs in the submission
- ☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*
- ☐ Yes, a redacted copy of the complete submission
- ☐ Yes, a redacted copy of part(s) of the submission
- ☐ No

PART IV – INTENDED USE

1. Describe the intended use of the notified substance including the foods in which the substance will be used, the levels of use in such foods, the purpose for which the substance will be used, and any special population that will consume the substance *(e.g., when a substance would be an ingredient in infant formula, identify infants as a special population).*

Oat β-glucan is intended for use as a source of dietary fiber for general addition to all foods except infant formula and meat and poultry products.

2. Does the intended use of the notified substance include any use in meat, meat food product, poultry product, or egg product? *(Check one)*
☐ Yes ☒ No

PART V – IDENTITY

1. Information about the Identity of the Substance

	Name of Substance[1]	Registry Used *(CAS, EC)*	Registry No.[2]	Biological Source *(if applicable)*	Substance Category *(FOR FDA USE ONLY)*
1	beta-glucan of any origin such as oats, barley, wheat	CAS	9041-22-9	Oats	
2	mixed-linkage (1-3),(1-4)-beta-D-glucan	CAS	55965-23-6		
3					

[1] Include chemical name or common name. Put synonyms *(whether chemical name, other scientific name, or common name)* for each respective item (1 - 3) in Item 3 of Part V *(synonyms)*

[2] Registry used e.g., CAS *(Chemical Abstracts Service)* and EC *(Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))*

2. Description

Provide additional information to identify the notified substance*(s)*, which may include chemical formula*(s)*, empirical formula*(s)*, structural formula*(s)*, quantitative composition, characteristic properties *(such as molecular weight(s))*, and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source *(e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source)*, and include any known toxicants that could be in the source.

Oat-derived beta-glucan manufactured to meet the specifications on page 11 in Table 1.
Chemical structure is provided on page 9.
Finished product weight-average molecular weight of PromOat® is 2,000 kDa. See page 9.
Chemical formula is (C6H10O5)n. See page 8.

3. Synonyms

Provide as available or relevant:

1	• β-D-glucan • (1-3),(1-4)- β-D-glucan • β-D-glucosylglucan
2	PromOat® or PromOat® Beta Glucan
3	

PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

(check list to help ensure your submission is complete – check all that apply)

- ☒ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☒ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☐ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

PART VII – SIGNATURE

1. The undersigned is informing FDA that Tate & Lyle *(name of notifier)*

has concluded that the intended use*(s)* of Oat beta-glucan *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ Tate & Lyle *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

Tate & Lyle *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

5450 Prairie Stone Parkway, Hoffman Estates, Illinois 60192 *(address of notifier or other location)*

Tate & Lyle *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

OR

☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ---------- *(GRAS Affirmation Petition No.)*

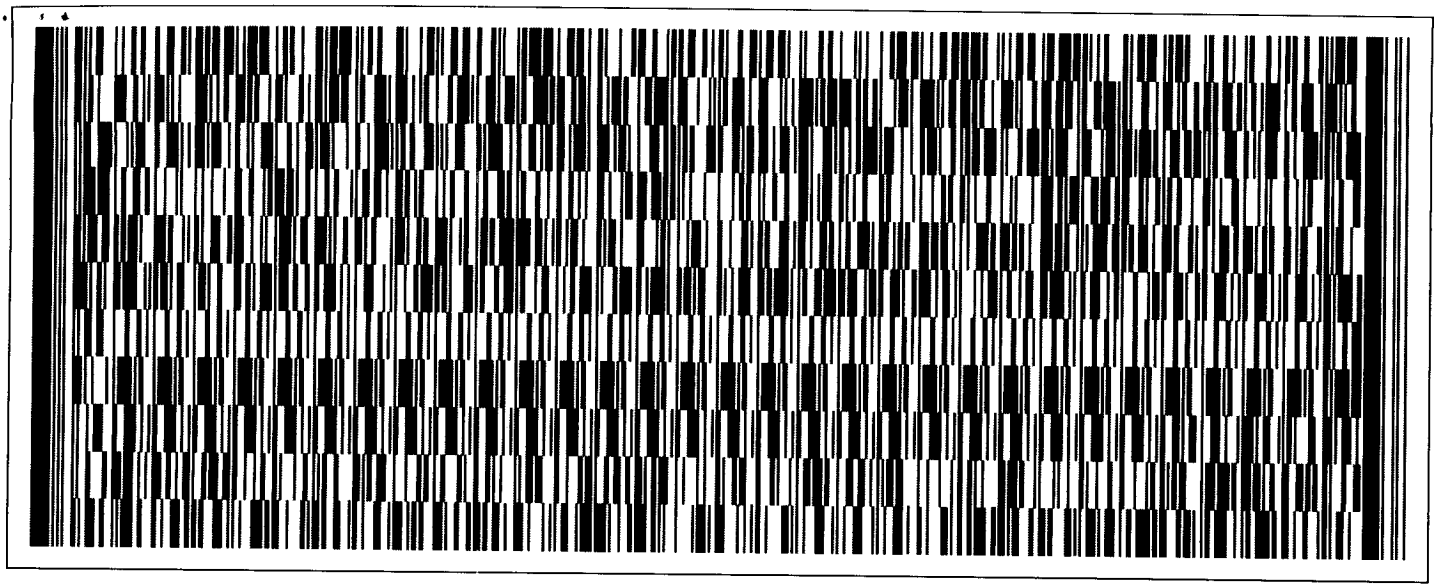
3. Signature of Responsible Official, Agent, or Attorney	Printed Name and Title	Date (mm/dd/yyyy)
(b) (6) [redacted]	onald F. Schmitt, Senior Managing Scientist	09/15/2014

PART VIII – LIST OF ATTACHMENTS

List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Appendix A - Certificates of Analysis - Characterization	pp. 44-53
	Appendix B - Technical Product Sheets/Data Sheets	pp. 54-57
	Appendix C - Stability Test Results	pp. 58-59
	Exhibit 1 - Report of the Expert Panel	pp. 60-66

OMB Statement: Public reporting burden for this collection of information is estimated to average 150 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services,Food and Drug Administration, Office of Chief Information Officer, 1350 Piccard Drive, Room 400, Rockville, MD 20850. (Please do NOT return the form to this address.). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.



GRAS Determination of Oat Beta-Glucan for Use in Food

SUBMITTED BY:

Tate & Lyle
5450 Prairie Stone Parkway
Hoffman Estates, IL 60192

SUBMITTED TO:

U.S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
HFS-200
5100 Paint Branch Parkway
College Park MD 20740-3835

CONTACT FOR TECHNICAL OR OTHER INFORMATION

Donald F. Schmitt, MPH
ToxStrategies, Inc.
739 Thornapple Drive
Naperville, IL 60540

September 7, 2014

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Table of Contents

1.0. GRAS Exemption Claim 5

2.0 Description of Substance 8
- A. Identity 8
- B. Common Name 8
- C. Formal/Chemical Names 8
- D. Trade Names 8
- E. Chemical/Structural Formulas 8
- F. Manufacturing Process 9
- G. Product Specifications 11
- H. Stability Data for Oat β-Glucan 13

3.0 History of Use/Regulatory Approval of Oat β-Glucan 13

4.0 Intended Use and Estimated Intake (EDI) 15

5.0 Safety 16
- A. Introduction 16
- B. Safety Data 16
- 1. Absorption, Distribution, Metabolism, and Excretion (ADME) 17
  - Animal studies 17
  - Human studies 17
- 2. Toxicological Studies 18
  - Animal Studies 18
  - Short-term studies 18
  - Genotoxicity 20
- 3. Human Studies on Beta-Glucan 21
  - Studies of the Cholesterol-Lowering Effect of Beta-Glucan 22
  - Studies of the Modulation of Blood Glucose and Insulin by Beta-Glucan 26
  - Studies of Immune-Modulating Effects of Beta-Glucan 29
  - Additional Protective Effects of Beta-Glucan 29
  - Tolerance Studies in Human Volunteers 30
  - Interaction with Nutrient Absorption 30
  - Allergenicity 31

6.0 Basis for the GRAS Determination 34
- A. Introduction 34
- B. Safety Determination 34
- C. General Recognition of the Safety of Oat Beta-Glucan 35

7.0 References 38

8.0 Appendices 44

Appendix A. Certificates of Analysis – Characterization 45

Appendix B. Technical Product/Data Sheets 54

Appendix C. Stability Test Results 58

Exhibit I. Report of the Expert Panel 60

List of Acronyms

ADME	absorption, distribution, metabolism, and excretion
AUC	area under the curve
BMI	body mass index
bw	body weight
B-G	beta-glucan
C	centigrade
cGMP	current Good Manufacturing Practice
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
COA	certificate of analysis
CT	computed topography
CVD	cardiovascular disease
dL	deciliter
DNA	deoxyribonucleic acid
DRV	dietary reference value
EFSA	European Food Safety Authority
FDA	Food and Drug Administration
g	gram
GI	gastrointestinal
GLP	Good Laboratory Practice
GMO	genetically modified organism
GMP	Good Manufacturing Practice
GRAS	Generally Recognized as Safe
GRNs	Generally Recognized as Safe Notifications
h	hour
HDL	high-density lipoprotein
IgG	immunoglobulin G
IgM	immunoglobulin M
IOM	Institute of Medicine
i.p.	intraperitoneal
IU	International Units
IV	intravenous
JHCI	United Kingdom Joint Health Claims Initiative
kDa	kilodalton
kg	kilogram
L	liter
LDL	low-density lipoprotein
mg	milligram
mL	milliliter
mmol	millimole
MoAb	monoclonal antibody
PO	per oral

SCFA	short-chain fatty acid
TEF	thermic effect of food
TGL/TAG	triglyceride/triacylglycerol
ug	microgram
US	United States
VLDL	very low-density lipoprotein
WMD	weight mean difference

4

1.0. GRAS Exemption Claim

A. Name and Address of Notifier

Tate & Lyle, through its agent ToxStrategies, Inc., hereby notifies the Food and Drug Administration that the use of the identified oat β-glucan product described below and which meets the specifications described herein is exempt from pre-market approval requirements of the Federal Food, Drug, and Cosmetic Act because Tate & Lyle has determined that such use is generally recognized as safe (GRAS) through scientific procedures.

(b) (6)

09/15/2014

Donald F. Schmitt, M.P.H.
Senior Managing Scientist
ToxStrategies, Inc.
Agent for Tate & Lyle

Date

B. Name of GRAS Substance

The name of the substance that is the subject of this GRAS determination is PromOat® Beta-Glucan, a β-glucan from oat bran.

C. Intended Use in Food

Oat-derived β-glucans are intended for use as a source of dietary fiber for general addition to all foods except infant formula and meat and poultry products. It will be added to the same foods at per serving levels as identified in the oat and barley β-glucan GRAS Notification submissions to the U.S. FDA (all received "no objection letters", GRNs 207, 344, and 437). The amount used will not exceed the amount reasonably required to accomplish its intended technical effect.

D. Basis for GRAS Determination

This Assessment documents the evidence of the safety and the "Generally Recognized As Safe" (GRAS) status of the proposed uses of Tate & Lyle's oat-derived β-glucan product (PromOat®). It consists of an evaluation of the safety and the GRAS status of the proposed uses of this ingredient, and the conclusion by a panel of experts (Expert Panel) qualified by scientific training and experience to evaluate the safety of substances added to food that the proposed uses of Tate& Lyle's β-glucan ingredient are safe and GRAS as determined by scientific procedures.

Tate & Lyle's GRAS determination for the intended use of oat-derived β-glucan is based on scientific procedures as described under 21 CFR § 170.30(b). The intended use of the oat β-glucan preparation has been determined to be safe, and Generally Recognized as

Safe (GRAS) and the safety of intake exposure under the proposed conditions of use is based on knowledge and information that is both publicly available and widely accepted by experts qualified by scientific training and experience to evaluate the safety of substances in food. The publicly available safety data combined with the widely disseminated knowledge concerning the chemistry of β-glucan from various sources such as oats, barley, and yeast combined with the long history of approval/use of such ingredients provide a sufficient basis for an assessment of the safety of oat-derived β-glucan for the uses proposed herein.

To date, the FDA has issued "no questions" letters in response to three Generally Recognized As Safe (GRAS) Notifications (GRNs) on β-glucan preparations from oat and barley sources (FDA, 2006, 2011, 2013). In addition to containing reviews of the published safety information, the GRNs included expert panel reports that reviewed and discussed in detail the metabolism, toxicology, and human health and safety data for β-glucan. Based on these GRAS notifications, FDA currently permits the use of β-glucan preparations from a variety of sources at the use-levels indicated in the notifications.

As noted in the GRNs cited above, there is a long history of safe use of oats and products derived from oats such as oat β-glucan concentrates. Other natural sources of β-glucan concentrates such as barley have been safely consumed for decades. In addition, β-glucan is not absorbed to any significant degree because of its large molecular size. While there is a noted lack of published safety studies of oat β-glucan concentrates, the safety section herein describes numerous animal and human safety studies of barley β-glucan which is similar to oat β-glucan, as both contain polysaccharides of unbranched, linear, mixed-linkage (1-3)(1-4)-β-D-glucan. These studies support the safe use of oat β-glucan for the proposed uses.

The focus of this GRAS self-determination is for an identical general food use of oat-derived β-glucan (excluding infant formula, medical foods, and meat and poultry) as current barley- and oat-derived β-glucan products as described in GRN 207, 344, and 437 (FDA, 2006; FDA, 2011; FDA, 2013). Cargill, in GRAS Notification 344, estimated the combined average intake of barley betafiber by consumers from all uses of barley betafiber (i.e., general food use and meat and poultry) would be 12.4 g/person/day (8.7 g β-glucan/person/day). The 90th percentile intake was estimated to be 23.5 g/person/day (16.5 g β-glucan/person/day). Cargill stated that barley betafiber would be added to food at levels of 4.3 g/serving, resulting in approximately 3 g of β- glucan/serving. Given the lower level of β-glucan (approximately 35%) in Tate & Lyle's PromOat® product, the estimated intake of β-glucan from the proposed uses of Tate & Lyle's product will be lower by approximately 50% (i.e., 4.35 and 8.25 g β-glucan/person/day for the mean and 90th percentile, respectively). While Tate & Lyle's PromOat® product could be added at a higher per serving level, the use of oat β-glucan in this manner is considered to be self-limiting for technological reasons such as product texture and/or flavor profile. In addition, since use in meat and poultry is not being considered as part of this GRAS Notification, the resulting estimated intake will be less than the current GRAS oat- and barley-derived β glucan products that were the subject of GRN Nos. 207, 344, and 437. In summary, the proposed uses of PromOat® will not result in an increase in the overall

consumption of β-glucan, but simply provide an alternative source of β-glucan for use in food.

Numerous studies have been conducted and published in support of the evaluation of the safety of barley β-glucan, including *in vitro* and *in vivo* animal studies as well as clinical studies in humans. While there is a lack of published preclinical safety studies on oat β-glucan, products containing oat β-glucan concentrates have been employed in numerous clinical trials. Other than mild, transient gastrointestinal (GI) effects such as flatulence and abdominal discomfort, no significant adverse effects were noted. It should be noted that these GI effects commonly occur following a shift from a low- to high-fiber diet. Evaluation of the possible effects of oats, cereal fiber and/or β-glucan on mineral absorption and allergenicity have also been considered by the U.S. FDA and the European Food Safety Authority (EFSA) and found not to present a significant safety concern as consumed as part of the normal diet.

Determination of the safety and GRAS status of this oat-derived β-glucan preparation described above for direct addition to food under its intended conditions of use was made through deliberation of an Expert Panel consisting of Michael Carakostas, DVM, Ph.D., Carol A. Knight, Ph.D., and Stanley M. Tarka, Jr., Ph.D, who reviewed a dossier prepared by ToxStrategies as well as other information available to them. These individuals are qualified by scientific training and experience to evaluate the safety of food and food ingredients. They individually and collectively critically evaluated published data and information pertinent to the safety of oat-derived β-glucan, and unanimously concluded that the intended use of oat β-glucan in food, produced consistent with cGMP and meeting appropriate specifications, as delineated above is "generally recognized as safe" ("GRAS") based on scientific procedures.

E. Availability of Information

The data and information that serve as the basis of this GRAS determination, as well any information that has become available since the GRAS determination, will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times from ToxStrategies, Inc., Naperville, IL.

2.0 Description of Substance

A. Identity

Oat β-glucan (beta-glucan) is a natural soluble dietary fiber ingredient derived from oat grain and is rich in {1-3,1-4} β-glucan.

B. Common Name

Oat β-glucan.

C. Formal/Chemical Names

The chemical names and synonyms for oat β-glucan include the following:

- β-D-glucan
- (1-3),(1-4)- β-D-glucan
- β-D-glucosylglucan

The Chemical Abstracts Service (CAS) Registry Number for β-D-glucans of any origin is 9041-22-9 (e.g., barley, oat, mushroom, wheat, and yeast). The CAS number for the mixed-linkage (1-3),(1-4)-β-D-glucan is 55965-23-6.

D. Trade Names

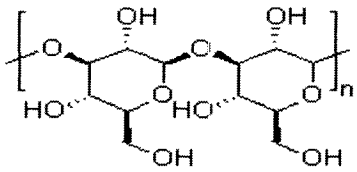
The trade name of Tate & Lyle's oat β-glucan is PromOat® or PromOat® Beta Glucan.

E. Chemical/Structural Formulas

Oat β-glucan consists of polysaccharides of unbranched, linear, mixed-linkage (1-3),(1-4)-β-D-glucans. Oat and barley derived β-glucans contain approximately 70% (1-4) linkages and 30% (1-3) linkages (Woodward and Fincher, 1983; Saulnier et al., 1994; FDA, 2011; FDA, 2013). Typically, blocks of three or four (1-4)-linked β-glucosyl units are connected by (1-3) linkages. Oat-derived β-glucan appears to consist of higher tetrasaccharide and fewer trisaccharide building blocks and may have a higher molecular weight than β-glucan from barley. Furthermore, wheat-derived β-glucan contains an even greater amount of trisaccharides compared to barley-derived β-glucan. In other words, the composition of β-glucans from oat, barley, and wheat form a continuum (FDA 2011, 2013). However, the respective differences are rather small and are unlikely to produce physiological differences (FDA, 2011; FDA, 2013).

The molecular formula for β-D-glucan is $(C_6H_{10}O_5)n$ and the molecular structure can be

found below.



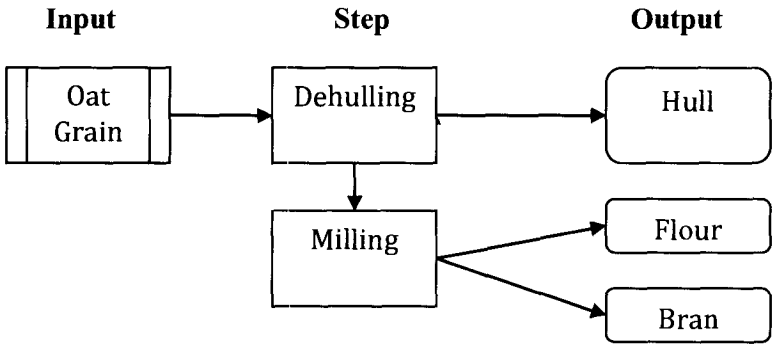
The molecular weight of the oat β-glucan present in commercially available processed food preparations ranges from about 100 kDa to 2000 kDa (EFSA, 2010). The finished product weight-average molecular weight of PromOat® is 2,000 kDa.

F. Manufacturing Process

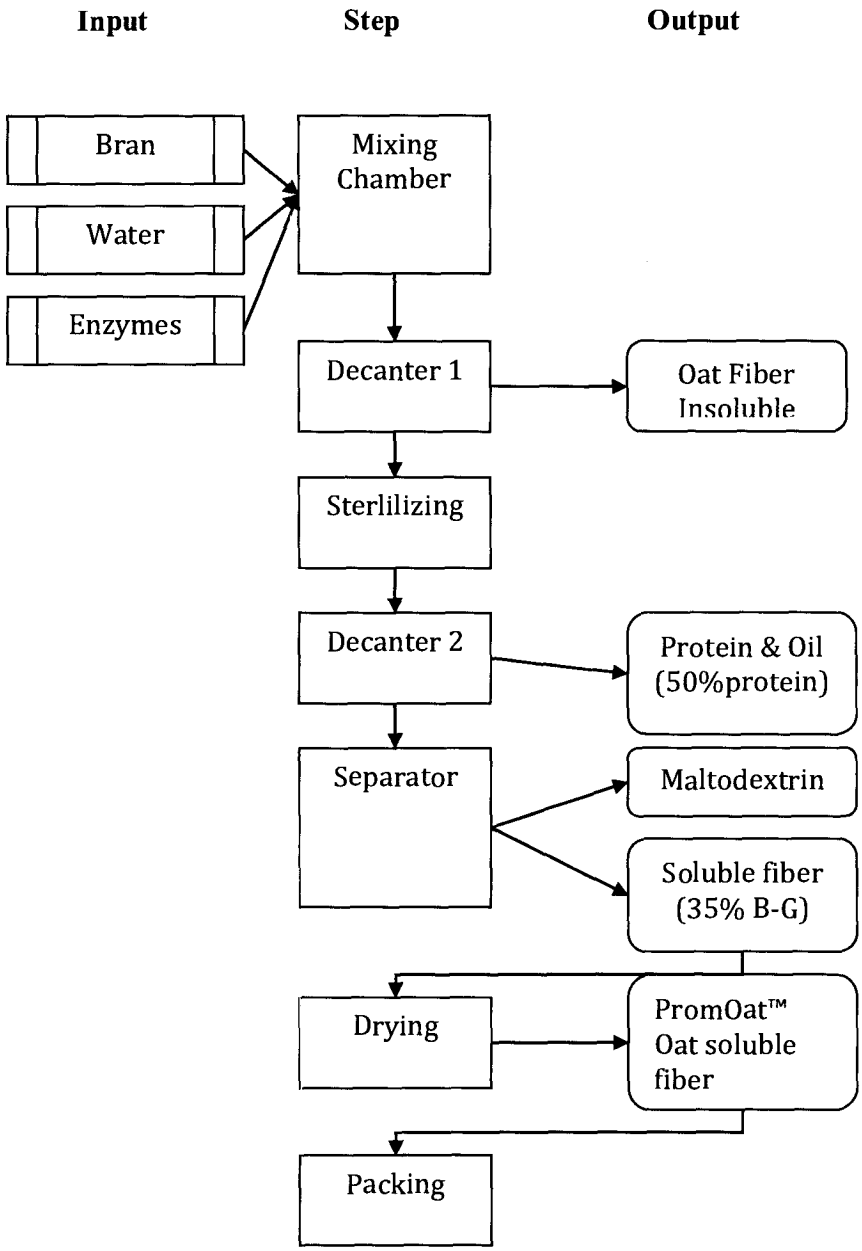
Tate & Lyle's PromOat® product that is the subject of this GRAS self-determination is manufactured in a two-step process. It is manufactured following current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110). The first-step is a dry mill process in which the oat grain is dehulled (husk and most of endosperm separated) and milled to specifications. The final output of the dry milling process is oat bran, which is employed in the second processing step, a wet process. In the wet fractionation process, the oat bran is mixed with water and food use-approved enzymes from non-GMOs (genetically modified organisms) at specified temperatures. The mixture is passed through physical separation procedures and sterilized. The process output is insoluble fiber, protein, oat oil, maltodextrin (approved in 21 CFR §184.1444), and oat soluble fiber rich in β-glucan. The maltodextrin and oat soluble fiber (35% β-glucan) components comprise the PromOat® product (see Step 2 below).

A flow diagram of Tate & Lyle's manufacturing process can be found below.

Step 1. Dry Process



Step 2. Wet Process



Reagents/processing aids used in the manufacture of oat β-glucan are limited to water and the enzyme alpha-amylase which is commonly used in food ingredient manufacturing processes. No chemical processing aids are employed in Tate & Lyle's manufacturing process. The alpha-amylase enzyme preparation employed in the process is GRAS per

21 CFR §184.1012, complies with Food Chemical Codex specifications, and is used at levels not to exceed current good manufacturing practice.

G. Product Specifications

Food grade specifications for Tate & Lyle's oat β-glucan (PromOat®) are presented in Table 1. The typical β-glucan content of PromOat® is 33-36% on a dry matter basis. PromOat® is a fine, cream-colored powder. Analytical results from three non-consecutive lots are provided in Appendix A. A comparison of three non-consecutive lots of β-glucan to the specifications below can be found in Table 2.

Table 1. Specifications for Oat Beta-Glucan (PromOat®)

Parameter (Assay Method)	Specification
Physical Characteristics	
Appearance (Visual)	Fine, cream colored powder
Moisture (IDF Standard 4A 1982)	Typically, 4-6% on a dry basis
β-D-glucan (AOAC 995.16)	33-36%, on a dry basis
Heavy Metals*	
Lead (NMKL No 161 1998)	≤ 0.1 ppm
Arsenic (NMKL No 161 1998)	≤ 0.1 ppm
Cadmium (NMKL No 161 1998)	≤ 0.1 ppm
Mercury (NMKL No 161 1998)	≤ 0.1 ppm
Microbiological Analyses	
Total plate count (NMKL No 86 1999)	<1000 cfu/g
Enterobacteriaceae (NMKL No 144 2000)	<10 cfu/g
Staphylococcus aureus (NMKL No 66, 3 ed, 1999 modified)	<20 cfu/g
Yeasts (IDF 94B; 1990 modified)	<100 cfu/g
Molds (IDF 94B; 1990 modified)	<100 cfu/g
Salmonella (NMKL No 71, 5 ed, modified)	Negative/25g
E.coli (NMKL No 125, 3 ed, 1996)	Negative

* It should be noted that heavy metals levels are not routinely reported on COAs (see Appendix A), but are documented in routinely conducted analytical reports which are also included in Appendix A.

Table 2. Analytical Results for 3 Lots of Oat Beta-Glucan (PromOat®)

Specification		Lot No. 1326	Lot No. 1344	Lot No. 1411
β-D-glucan	33-36%, on a dry basis	34.0	35.0	34.0
Moisture	4-6%, on a dry basis	5.3	5.7	6.0
Heavy Metals*				
Lead	≤ 0.1 ppm	<0.020	<0.020	<0.020
Arsenic	≤ 0.1 ppm	<0.010	<0.010	<0.010
Cadmium	≤ 0.1 ppm	<0.050	<0.050	<0.050
Mercury	≤ 0.1 ppm	<0.020	<0.020	<0.020
Microbiological Analyses				
Total plate count	<1000 cfu/g	<500	<600	<100
Enterobacteriaceae	<10 cfu/g	<10	<10	<10
Staphylococcus aureus	<20 cfu/g	<20	<20	<20
Yeasts	<100 cfu/g	<60	<20	<20
Molds	<100 cfu/g	<80	<80	<20
Salmonella	Negative/25g	Neg/25g	Neg/25g	Neg/25g
E.coli	Negative	Negative	Negative	Negative

* Heavy metals levels are not routinely reported on COAs (see Appendix A), but are documented in routinely conducted analytical reports which are also included in Appendix A.

Typical compositional and nutritional analyses of Tate & Lyle's PromOat® product containing 33-36% β-glucan are presented in Table 3.

Table 3. Nutritional Analyses of PromOat®

Nutrient	Amount
Calories (kcal/100g)	315
Protein (g/100g)	4.0
Total fat (g/100g)	0.5
Saturated fat (g/100g)	<0.1
Carbohydrate (oat maltodextrins) (g/100g)	56
Total Dietary Fiber (g/100g)	36-38

Soluble Fiber (g/100g)	35
Sugars (g/100g)	<0.5
Iron (mg/100g)	0.32
Sodium (mg/100g)	<25 mg
Cholesterol (mg/100g)	<1.0
Calcium (mg/100g)	9
Vitamin A Retinol (IU/100g)	<50
Vitamin C (mg/100g)	<1.0

The analytical (chemical and microbiological) results for oat β-glucan summarized in the above tables and included in the COAs and Technical Data Sheets in Appendices A and B confirm that the finished product meets the analytical specifications, demonstrates that the PromOat® manufacturing process results in a consistently reproducible product, and confirms the lack of impurities/contaminants (e.g., heavy metals, pesticides, microbiological toxins).

H. Stability Data for Oat β-Glucan

Tate & Lyle's oat β-glucan product PromOat® meets the above analytical specifications. Stability testing of PromOat® has been conducted at room temperature, 0°C, and 40°C for up to 18 months. After an 18-month storage period under a variety of storage conditions, PromOat® was found to be stable in terms of protein content, dry matter, β-glucan content, molecular weight, pH, appearance, color, smell, taste, volumetric weight (density), and microbiological parameters. Stability test results can be found in Appendix C.

3.0 History of Use/Regulatory Approval of Oat β-Glucan

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2013). Numerous food products containing oats are currently marketed in the U.S. and around the world. Oat fiber has become a desirable ingredient for addition to a variety of food products as a source of dietary fiber.

Epidemiological studies and clinical trials have consistently revealed that fiber-rich diets are associated with significant reductions in cardiovascular disease risk. While there is no established dietary reference value (DRV) for soluble fiber, the amount of soluble fiber in a typical mixed diet is one-fourth to one-third of the total dietary fiber intake (ADA, 2008; FDA, 2013).

Dietary Guidelines for Americans (HHS/USDA, 2005) recommend that adults eat half their grains as whole grains, which include oats and wheat. Adequate intake recommendations for adults (≤ 50 years of age) are 38g total dietary fiber/day for men and 25g total dietary fiber/day for women (IOM, 2005). For adults greater than 50 years of age, IOM recommends 30 g/day and 21 g/day for men and women, respectively. The guidelines also note that most Americans need to increase their intake of dietary fiber (HHS/USDA, 2005). The daily reference value for dietary fiber is 25 g for a 2000 calorie diet per 21 CFR § 101.9(d).

Oat β-glucan is found in the cell walls of oat kernels. Beside oats, β-glucan is consumed from other cereals and edible plants such as barley, rye, and wheat. Oat-derived β-glucan concentrates (e.g., Oatrim with a β-glucan content of up to 10% and OatVantage™ with 54% β-glucan) are marketed in the United States and have GRAS status (FDA, 2011; FDA, 2013). Quaker Oats self-determined the GRAS status of Oatrim in 1992 (FDA, 2011). As described in GRAS Notification No. 437 (FDA, 2013), the GRAS status of Oatrim was supported by several factors including: 1) Oatrim's similarity to oat starch and maltodextrin (food ingredients with a known safety use profile), 2) the enzymatic manufacturing process was analogous to the biological digestion of starch by humans, and 3) short-term toxicity studies and safety evaluations of Oatrim's constituents did not reveal any areas of concern (FDA, 2011; FDA, 2013). OatVantage™ has similarly been on the market for 10+ years and no safety concerns have been reported.

The U.S. FDA and European Food Safety Authority (EFSA) have reviewed the association of soluble fiber from oats and the reduced risk of heart disease (21 CFR § 101.81) (62 FR 3584, January 23, 1997) and/or the maintenance of normal blood cholesterol concentrations (EFSA 2010). As described in Garuda's GRN No. 437 (FDA, 2013), in October 2002, in response to a petition jointly filed by the Quaker Oats Co. and Rhodia, Inc., FDA (2002) amended the 1997 health claim for soluble fiber from rolled oats to add an additional eligible source of whole oat β-glucan soluble fiber, the soluble fraction of α-amylase-hydrolyzed oat bran or whole oat flour with a β-glucan soluble fiber content at levels up to 10%. The agency concluded, based on the publicly available scientific evidence that---in addition to rolled oats, oat bran, and whole oat flour—the soluble fraction of α-amylase-hydrolyzed oat bran or whole oat flour with a β-glucan content up to 10% and not less than that of the starting material is an appropriate source of β-glucan soluble fiber for the health claim. Regarding safety, the petitioners determined their product to be GRAS, and the basis of the safety determination for their products (containing up to 25% β-glucan) was the similarity to other existing cereal adjuncts, such as pre-cooked flours, pre-cooked bran, and starches. Following its review, FDA concluded that the petitioners satisfied the preliminary requirement of 21 CFR § 101.14(b)(3)(ii) to demonstrate to FDA's satisfaction that the use of Oatrim, as described previously, is safe and lawful as a food ingredient at levels necessary to justify the health claim (FDA, 2011).

The FDA has also authorized a health claim for soluble fiber from whole grain barley and barley-containing products and coronary heart disease ("CHD") (21 CFR § 101.81)

(FDA, 2005). In August 2008, FDA published a final regulation authorizing barley betafiber as an eligible source of soluble fiber for this health claim (FDA, 2008). Barley soluble fiber-containing foods must provide at least 0.75 g of β-glucan soluble fiber per serving of the food. In 2008, the agency published a final regulation on the health claim regulation entitled "Soluble fiber from certain foods and risk of coronary heart disease (CHD)" to add barley betafiber as an additional eligible source of β-glucan soluble fiber. In support of the safety of barley-derived β-glucan (≥70%), the petitioner determined that its product was GRAS for the proposed uses. FDA also received two GRAS notices, GRN 207 and 344 (FDA 2006; FDA, 2011) on this subject and issued letters stating that the agency had "no questions" about the GRAS determination under the intended conditions of use.

EFSA also authorized a health claim regarding the maintenance of normal blood cholesterol concentrations for soluble cereal fibers, particularly β-glucan from oats (EFSA, 2010). In an opinion on the scientific substantiation of a health claim related to oat β-glucan and lowering of blood LDL and total cholesterol, the EFSA Panel concluded that a cause and effect relationship has been established between the consumption of oat β-glucan and lowering of blood LDL-cholesterol concentrations. For support of the health claim, the Panel recommended that foods should provide at least 3 g of oat β-glucan/day. In a previous health claim approval, EFSA (2009) also agreed to the following claim for β-glucan: maintenance of normal blood cholesterol concentrations and maintenance or achievement of a normal body weight.

To date, FDA has reviewed two GRAS Notifications of β-glucan from barley (FDA, 2006; FDA, 2011) and one from oats (FDA, 2013). Extensive published information and data on β-glucan were submitted. All of the GRAS notifications received "no questions" letters from the FDA. Tate & Lyle considers the information and study data described in these cited notifications as directly applicable to this notification. Furthermore, β-glucan derived from oats or barley contains polysaccharides of unbranched, linear, mixed-linkage (1-3), (1-4)-β-D-glucan, and from a physiological perspective, there is virtually no difference. Thus, from a safety perspective, the available studies of barley β-glucan and the studies described in GRNs 207, 344, and 437 are applicable to the safety assessment of oat β-glucan. No recent studies raising any new safety concerns have appeared in the published literature subsequent to these evaluations, particularly the most recent GRAS notice GRN 437.

4.0 Intended Use and Estimated Intake (EDI)

Estimated intake

The focus of this GRAS self-determination is for an identical general food use of oat-derived β-glucan (excluding infant formula, medical foods, and meat and poultry) to the current barley- and oat-derived β-glucan products as described in GRN 207, 344, and 437 respectively (FDA, 2006; FDA, 2011; FDA, 2013). Cargill, in GRAS Notification 344, estimated the combined average intake of barley betafiber by consumers from all uses of

barley betafiber (i.e., general food use, and meat and poultry) would be 12.4 g/person/day (8.7 g β-glucan/person/day). The 90th percentile intake was estimated to be 23.5 g/person/day (16.5 g β-glucan/person/day). Cargill stated that barley betafiber would be added to food at levels of 4.3 g/serving, resulting in approximately 3 g of β-glucan/serving. Given the lower level of β-glucan (approximately 35%) in Tate & Lyle's PromOat® product, the estimated intake of β-glucan from the proposed uses of Tate & Lyle's product will be lower by approximately 50% (i.e., 4.35 and 8.25 g β-glucan/person/day for the mean and 90th percentile, respectively). In addition, since use in infant formula, medical foods, and meat and poultry is not being considered as part of this GRAS Notification, the resulting estimated intake will be less than the current GRAS oat- and barley-derived β glucan products that were the subject of GRN Nos. 207, 344, and 437. In summary, the proposed uses of PromOat® will not result in an increase in the overall consumption of β-glucan, but simply provide an alternative source of β-glucan for use in food. Therefore, cumulative intake analysis is not considered necessary.

Self-limiting use

While Tate & Lyle's PromOat® product could be added at a higher per serving level, the use of oat β-glucan in this manner is considered to be self-limiting for technological reasons such as product texture and/or flavor profile.

5.0 Safety

A. Introduction

Tate & Lyle currently markets oat β-glucan (PromOat®) outside of the U.S. Both EFSA and the U.S. FDA have reviewed the safety of oat β-glucan and other cereal β-glucan sources, such as barley, and found their use to be safe based upon the available animal, *in vitro*, and human safety data. The published data, as well as reviews conducted by regulatory agencies, support the conclusion that β-glucan, and in particular oat-derived β-glucan, is safe for use as a human food ingredient.

B. Safety Data

Beta-glucan from a variety of sources including barley and oats has been the subject of numerous published scientific evaluations and regulatory reviews (e.g., FDA, 2006, 2011, 2013). These data and regulatory submissions form the basis of the safety summary presented below and are considered directly applicable to this GRAS notification. The available animal and human metabolism and safety/toxicity information indicate that β-glucan from all sources will be similarly metabolized/handled by the body following consumption.

A summary of the most relevant studies on β-glucan metabolism and toxicity along with clinical and epidemiological studies is presented below.

1. Absorption, Distribution, Metabolism, and Excretion (ADME)

Oat β-glucan is a dietary fiber and is resistant to digestion by mammalian enzymes, passing into the large intestine mostly intact once ingested (IOM, 2005). While the fermentation quality of dietary fibers range widely in the large intestine, soluble fiber, such as β-glucan, is highly fermentable by bacteria in the colon to carbon dioxide, methane, hydrogen, and short-chain fatty acids (SCFAs) (IOM, 2005). Several studies in animals and humans characterizing the degradation of β-glucan in the gastrointestinal tract are reported below.

Animal studies

Berggren et al. (1993) examined cecal SCFA content, cecal pH, fermentability, and dry matter digestibility in Wistar rats fed diets containing different nondigestible components including barley β-glucan. The authors reported that β-glucan was highly fermentable (>90%) and resulted in one of the largest pool sizes of short-chain fatty acids. β-glucan (as well as oat bran) diets were associated with low dry matter digestibility (~93%) compared to the other diets. Knudsen et al. (1993) studied the effect of oat β-glucan on digestion and metabolism of polysaccharides in ileum-cannulated pigs (n=4/group) using diets containing 22-76 g/kg oat β-glucan. Digestibility of β-glucan was 17-31% in the ileum and 100% in the feces.

Dongowski et al. (2002) demonstrated very high fermentability of β-glucan in male rats. Animals were fed a control diet for 1 week followed by 1 of 4 barley diets (groups A-D) or the control diet for 6 weeks (n=10/group; 5 groups total). The control diet contained 0.03% β-glucan and 0.45% resistant starch, and the 4 test diets contained various amounts of β-glucan (~4-6%) and resistant starch (~4-12%). β-glucan was detected in stomach and small intestine contents, at much lower concentrations in the cecum and colon contents, but not in the feces, indicating complete fermentation. Rats on barley test diets also had significantly higher concentrations of SCFAs in feces compared to controls.

Human studies

Robertson et al. (1997a) evaluated the effect of barley-based flapjacks (5.6 g β-glucan, of which 1.6 g was soluble) on the ileal contents of ileostomy patients. Ileal contents recovered after 12 hours contained 3.64 g β-glucan, approximately 65% of what was consumed. The ileal β-glucan was approximately 60% soluble, an increase from the test meal (~28%), indicating that solubility increased with passage through the small intestine. The authors indicated that this was likely due to digestive activities of proteolytic enzymes on the barley product, which was further supported by tests *in vitro*. Additionally, the authors reported that the proportion of lower molecular weight β-glucans was likely increased in the ileal contents. Robertson et al. (1997b) conducted a similar study, with findings consistent with Robertson et al. (1997a), showing that "unextractable" β-glucans in barley can be solubilized in the upper gut and serve as a source of dietary fiber.

Sundberg et al. (1996) likewise showed that there is a depolymerization of β-glucan as it transits through the upper gastrointestinal tract. In this study, 9 ileostomy patients received 4 different diets, in random order, which differed only in the type of bread: oat bread, oat bread with β-glucanase ("enzymatic oat"), barley bread, or wheat bread corresponding to β-glucan intakes of approximately 12.5, 4, 12.9, or 1.1 g, respectively. In the oat, enzymatic oat, and barley breads, about 50% of β-glucan was soluble. In those consuming oat or barley breads, 81-87% of β-glucan intake was excreted in ileal samples whereas individuals eating enzymatic oat and wheat breads had excretions of 58 and 36%, respectively. The peak molecular weight of the β-glucan excreted from individuals consuming the oat bread was notably lower than the β-glucan in the original oat bread indicating that depolymerization was taking place. However, the authors also noted that degradation was known to occur in the ileostomy bags, and so care should be taken when interpreting these results.

Hughes et al. (2008) evaluated the fermentation of barley and oat β-glucans by human fecal microbiota *in vitro*. Three barley-derived β-glucan fractions (average molecular weights of 243, 172, and 137 kDa) and two oat-derived β-glucan fractions (average molecular weights of 230 and 150 kDa) were added to human fecal samples in pH-controlled anaerobic batch culture fermenters and SCFAs and lactic acid were measured. The mean SCFA ratio for all β-glucan treatments at 24 hours was 51:32:17 acetate: propionate: butyrate, which the authors reported to be propionate-rich. In general, beta-glucans displayed no apparent prebiotic potential.

2. Toxicological Studies

Animal Studies

Short-term studies

Dongowski et al. (2002) evaluated the physiologic effects of diets containing barley extrudates (containing β-glucan and resistant starches) in the intestines of male rats. Animals were fed a control diet for 1 week followed by 1 of 4 barley diets (groups A-D) or the control diet for 6 weeks (n=10/group; 5 groups total). The control diet contained 0.03% β-glucan and 0.45% resistant starch, and the 4 test diets contained various amounts of β-glucan (~4-6%) and resistant starch (~4-12%). The authors reported that all diets were well accepted by the rats and there were no treatment-related changes in appearance or behavior. However, colon and cecum weight were significantly greater in rats on test diets, which the authors attributed to the β-glucan content.

Delaney et al. (2003a) evaluated the toxicity of a water-extracted, β-glucan-enriched, soluble barley fiber (barley betafiber) in a 28-day feeding study in Wistar rats conducted according under Good Laboratory Practice (GLP) and according to OECD Guideline 407. Animals (n=5/group/sex) were given 1, 5, or 10% barley betafiber (0.7, 3.5, or 7% β-glucan) in a modified rodent diet as a replacement for pregelatinized potato starch (digestible carbohydrate), or a starch control diet for 28 days. Mean β-glucan intakes were determined to be 0.55, 2.9, and 5.6 g/kg-bw/day. All rats survived until scheduled

necropsy, and no treatment-related adverse effects were noted in general condition or behavior, growth, feed and water consumption, feed conversion efficiency, red blood cell or clotting potential parameters, clinical chemistry parameters, or organ weights. There were no abnormalities seen at necropsy or histopathology. Although clinical chemistry parameters (plasma urea, total protein, albumin, chloride, and calcium) exhibited slight changes, they were within the limits of historical controls and were not considered adverse. There was a dose-related increase in weight of full and empty cecum; however, this effect is typically seen in rodents on high fermentable, poorly digestible carbohydrate diets and is not considered toxicologically relevant. Increased total white blood cell counts were observed in males, which the authors attributed to increased peripheral lymphocytes as an indicator of β-glucan's immune modulating activity. This effect was not dose-dependent and only occurred in males at the low- and mid-dose levels. The authors concluded that daily consumption of concentrated amounts of barley β-glucan under the conditions of their study was not associated with signs of toxicity in Wistar rats.

Delaney et al. (2003b) conducted a similar study in CD-1 mice, a rodent species frequently used to evaluate inflammatory responses, to further investigate the potential for the immunological changes observed in rats to determine if any of these constitute an adverse effect. The study was conducted under GLP and according to a slightly modified OECD Guideline 407. Animals (n=12/group/sex) were given 1, 5, or 10% barley betafiber (0.7, 3.5, or 7 % β-glucan) in a commercial rodent diet as a replacement for pregelatinized potato starch (digestible carbohydrate), or a starch control diet for 28 days. Mean β-glucan intakes were determined to be 1.8, 9.3, or 19.0 g/kg-bw/day and 2.4, 11.6, or 23.6 g/kg-bw/day in males and females, respectively. Following 28 days, half the animals in each group were sacrificed for evaluation of clinical chemistry, hematology, and organ pathology, and the remaining mice were placed on the control diet for a 14-day recovery period. An additional (naïve) group (n=24/sex) consumed only the control diet and was used for hematological analysis given that the effect of multiple blood draws under the conditions of this study on hematology parameters was not known. Six mice from the naïve group/sex were sacrificed on days 0, 14, 27, and 41. Blood was collected from all animals prior to study initiation (day -2), from 6 animals/group/sex on days 14 and 27, and from the remaining recovery animals on days 27 and 41. No treatment-related adverse effects were seen in any sex or dose group at any time point. No treatment-related histopathologic changes were seen in primary immune organs or peritoneal immune organs. The authors concluded that daily consumption of concentrated amounts of barley β-glucan under the conditions of the study was not associated with treatment-related adverse effects in CD-1 mice, and further, that concentrated barley β-glucan is not likely to result in adverse immunological or inflammatory effects.

More recently, Jonker et al. (2010) conducted a 28-day oral toxicity study in Wistar rats using a high (75.6%) purity barley β-glucan (Glucagel™). The study was conducted according to OECD Guideline 407 and EC Guideline B.7. Animals (n=5/group/sex) were given 0 (control[1]), 1, 5, or 10% Glucagel™ in a modified rodent diet as a replacement for

[1] The control diet did not contain Glucagel™, but contained approximately 0.8% β-glucan from the basal diet.

pregelatinized potato starch (digestible carbohydrate), or a starch control diet for 28 days. Mean β-glucan intakes were 0.62, 3.0, or 5.8 g/kg-bw/day and 0.60, 3.1, or 5.9 g/kg-bw/day in males and females, respectively (based on 75.6% β-glucan in Glucagel™). Results were generally consistent with the 28-day study in rats conducted by Delaney et al. (2003a); the treatment was well-tolerated, and there were no adverse effects on general condition and appearance, neurobehavioral observations, growth, feed or water consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, or pathological findings. Cecal enlargement occurred in mid- and high-dose males, which the authors described as a non-specific, physiological response following ingestion of non-digestible carbohydrate and therefore was not toxicologically relevant. Lower plasma total cholesterol and phospholipids were noted in high-dose males. The authors stated that β-glucan has known cholesterol-lowering effects in animals and plasma lipids were within the normal range, and were therefore not considered toxicologically relevant. Also considered to be toxicologically insignificant, high-dose males had a slightly increased mean plasma urea result. All other test results for renal function were statistically and biologically unremarkable. Unlike the findings of Delaney et al. (2003a), increased circulating lymphocytes were not observed in the present study. The authors concluded that consumption of up to 10% Glucagel™ (5.8-5.9 g/kg-bw/day β-glucan) for 28 days was not associated with toxicity in Wistar rats.

Genotoxicity

Delaney et al. (2004) evaluated the genotoxicity of β-glucan (barley betafiber) in a standard *in vivo* bone marrow micronucleus assay in mice conducted under GLP and according to OECD Guideline 474. Male CD-1 mice (n=10/dose) were gavaged with barley betafiber in corn oil at doses of 74, 222, 666, or 2,000 mg/kg-bw. Half of the animals were sacrificed after 24 hours, the remaining after 48 hours. No clinical signs of toxicity were observed, so only the animals in the high dose group were evaluated and compared to negative and positive controls. No statistical increases in micronucleated polychromatic or normochromatic erythrocytes were observed. The authors concluded that barley betafiber was not clastogenic under the conditions of the study.

Several studies have evaluated the anti-genotoxic effects of β-glucans. Tohamy et al. (2003) evaluated the protective role of barley β-glucan against chromosomal aberrations in bone marrow and spermatogonial cells induced by anti-cancer drugs in CD-1 mice. β-glucan (100 mg/kg-bw) was administered i.p. to mice 24 hours prior to anti-cancer drug (cyclophosphamide, adriamycin, or cisplatin). Animals were sacrificed 24 hours following administration of the anti-cancer drug. Pretreatment with β-glucan significantly reduced the frequency of structural chromosomal aberrations induced by the three anti-cancer drugs in bone marrow and spermatogonial cells. The authors concluded that their results suggest that β-glucan plays a role in reducing the genotoxicity associated with chemotherapeutic drugs.

Angeli et al. (2006) investigated the clastogenic/anti-clastogenic potential of barley β-glucan in a chromosomal aberration assay using cells proficient or deficient in phase I and II enzymes (rat hepatoma HTC or Chinese ovarian CHO-k1 cells, respectively). Cells were incubated with β-glucan (2.5, 5, or 10 ug/L) and DNA damaging agents

(methylmethane sulfonates, 2-aminoanthracene, and arabinoside-3-phosphate) for 12 or 24 hours. No clastogenic effects were observed, and protective effects of β-glucan were evident even at the lowest dose tested. Similarly, Oliveira et al. (2006) evaluated the mutagenic activity of barley β-glucan (5, 10, or 20 ug/L) in a micronucleus assay in HTC or CHO-k1 cells. Only the highest dose (20 ug/L) showed mutagenic activity, which was seen in both cell lines. Antimutagenicity experiments were also conducted using methylmethane sulfonates and 2-aminoanthracene, with various types of β-glucan treatments at the same concentrations (pre-treatment, simultaneous treatment, or post-treatment). The authors reported that barley β-glucan showed desmutagenic and bioantimutagenic activities at varying doses, depending on the timing of treatment and the cell line.

Angeli et al. (2009) assessed the genotoxicity of barley β-glucan in a Comet assay in HepG2 cells. Cells were incubated with β-glucan (1, 5, 25, 100, or 200 μg/ml) for 24 hours. Cytotoxicity was observed at 200 μg/mL, and genotoxicity was observed in the 100 μg/mL dose group. The researchers also evaluated the protective effect of 1, 5, or 25 μg/mL β-glucan (administered pre-treatment, simultaneously, or post-treatment) on benzo(a)pyrene induced genotoxicity. Simultaneous treatment showed the greatest protective effect on genotoxicity, which was significant at 5 and 25 μg/L, but not at 1 μg/L. Cytotoxicity was significantly reduced at all concentrations tested. The authors reported that β-glucan possessed antimutagenic activity (mainly desmutagenic, but also bioantimutagenic).

3. Human Studies on Beta-Glucan

In 1997, FDA authorized the use of label health claims on the association between soluble fiber from whole oats and a reduced risk of coronary heart disease. The Federal Register Notice acknowledges the beneficial contribution from β-glucan (FDA, 1997):

> *Based on its review of evidence submitted with comments to the proposal, as well as of the evidence described in the proposal, the agency has concluded that the type of soluble fiber found in whole oats, i.e., beta (β)-glucan soluble fiber, is primarily responsible for the association between consumption of whole oats, including oat bran, rolled oats, and whole oat flour, and an observed lowering of blood cholesterol levels... (I)ntakes of β-glucan soluble fiber at or above 3 g per day were more effective in lowering serum lipids than lower intake levels.*

Published safety studies of oat β-glucan concentrates are lacking, however published clinical trials exist evaluating oat β-glucan in various types of food (e.g., beverages, breads, cereal, muffins) (FDA, 2013). Human studies evaluating oat-derived β-glucan and its effects are discussed herein, and a number of studies of barley- and wheat-derived β-glucan are also included.

In a recent article, Daou and Zhang (2012) reviewed advances in the beneficial health effects of oat β-glucan. Oat β-glucan has been shown to decrease total and low-density lipoprotein (LDL) cholesterol, improve high-density lipoprotein (HDL) cholesterol and

blood lipid profiles, attenuate postprandial glycemic and insulinemic responses in blood and help maintain body weight. By activating monocytes/macrophages and increasing the amounts of killer T-cells, NK cells and immunoglobulin, oat β-glucan can stimulate the immune system, which can improve the body's resistance to infectious and parasitic diseases as well as cancer.

Studies of the Cholesterol-Lowering Effect of Beta-Glucan

Soluble or viscous fibers, such as oat bran, have been shown to decrease serum cholesterol and low-density lipoprotein (LDL) cholesterol in humans. Oat bran has been shown to decrease high-density lipoprotein (HDL) cholesterol, but the difference is not significant (Anderson and Hanna, 1999).

Othman and coworkers (2011) evaluated recent studies to determine if recent investigations support previous conclusions by the FDA and United Kingdom Joint Health Claims Initiative (JHCI) that β-glucan soluble fiber from oats can decrease plasma cholesterol levels and the risk of heart disease. The authors found in their review that studies conducted during the past 13 years support the conclusion that oat β-glucan intake of at least 3 g/day may reduce plasma total- and LDL-cholesterol levels by 5-10% in both hypercholesterolemic and normocholesterolemic participants, with an average decrease of 5-7%. The authors concluded that scientific agreement continues to support a strong relationship between oat β-glucan and cholesterol levels, with newer information being consistent with earlier conclusions drawn by the FDA and JHCI.

In a 6-week randomized controlled trial using 87 men and women with mildly elevated cholesterol levels, Charlton and coworkers (2012) evaluated whether 1.5 g/d β-glucan consumed as ready-to-eat oat flakes was as effective in reducing blood cholesterol as 3.0 g/d β-glucan from oat porridge. Participants were assigned to 1 of 3 diet arms (25% energy protein; 45% energy carbohydrate; 30% energy fat): minimal β-glucan (control), 1.5 or 3.0 g β-glucan. Total cholesterol was significantly decreased in all groups (-7.8%, -7.2 % and -5.5% in the high, low and control groups, respectively), as was LDL (-8·4%, -8.5 % and -5.5 % in the high, low and control groups, respectively); however between-group differences were insignificant. The authors concluded that oat β-glucan intakes of 1.5 g/d were as effective as 3 g/d at lowering blood cholesterol.

In their meta-analysis of the literature and of unpublished trials on the cholesterol lowering effects of oat products, Ripsin et al. (1992) indicated that the addition of oat products to a diet yields a modest reduction in blood cholesterol level. For the 10 studies meeting the inclusion criteria, a summary effect size for change in blood total cholesterol level of -5.9 mg/dL (95% CI, -8.4 to -3.3 mg/dL) was calculated. The summary effect size for studies using wheat control groups was -4.4 mg/dL (95% CI, -8.3 to -0.38 mg/dL). The greatest reductions in blood cholesterol were seen in trials where participants had initially higher blood cholesterol levels (≥229 mg/dL). The authors concluded that their analysis provides strong support for the hypothesis that approx. 3 g/day soluble fiber from oat products can lower the total cholesterol level by 5-6 mg/dL. β-glucan concentrations were not specified.

Behall et al. (1997) conducted a crossover study to assess whether moderate amounts of oat fiber extract (concentrated β-glucan), often used as a fat replacer, would reduce plasma lipid concentrations and if it could be added to a typical diet. Twenty-three subjects (7 men, 16 women) with mildly elevated blood cholesterol consumed oat fiber extracts containing high (10%) or low (1%) β-glucan for 5 weeks after consuming a maintenance diet for one week. Total- and LDL-cholesterol were significantly lower after the oat fiber extract diets. However, compared to the maintenance diet, triglyceride levels, VLDL, HDL and HDL2 cholesterol did not significantly change. The authors concluded that modest amounts of oat extract in the diet produced significant reductions of cholesterol. Further, a significant dose response occurred between β-glucan and total cholesterol levels.

In a controlled, single-blind, randomized, cross-over trial, Beer et al. (1995) studied the effect of oat β-glucan on serum lipid concentrations in 14 healthy, hypercholesterolemic young men. Participants were assigned to a test group diet (oat gum instant whip, 9 g/day β-glucan) or a control group (placebo instant whip) for 14 days. After completion of the first diet, subjects switched to the alternate diet. Dietary intakes of the two groups were similar. The results indicated no significant effect of the oat gum on triglyceride, total- or LDL-cholesterol levels. HDL-cholesterol was significantly higher during consumption of the test diet. The authors concluded that in healthy young men oat gum's cholesterol-lowering ability is weak. Further, the authors concluded that the impact of oat bran products on cholesterol levels cannot be estimated by the β-glucan content, but instead by measuring the viscosity and solubility of the β-glucan.

Biorklund et al. (2005) performed a side-by-side comparison of the effects of beverages enriched with 5 or 10 g β-glucan from oats or barley on insulin and postprandial glucose concentrations and serum lipoproteins. The study was an 8-week single-blind, dose-controlled study using 5 parallel groups of 100 men and women with mildly elevated blood cholesterol levels. The study was conducted identically at two locations (the Netherlands and Sweden) and 89 persons (45 women, 44 men) completed the study. During an initial 3-week period, all participants consumed a control beverage containing rice starch. For the following 5-week period, 1 group consumed the control beverage and 4 groups consumed a beverage containing 5 or 10 g β-glucan from barley or oats. All participants consumed their own habitual diets. Blood samples were collected during weeks 0, 2, 3, 7 and 8 and analyzed for glucose, insulin, serum lipids and lipoproteins. Consumption of 5 g β-glucan from oats significantly lowered postprandial concentrations of glucose (30 min), insulin (30 min) and total cholesterol (7.4%). Consumption of 10 g β-glucan from oats did not significantly impact serum lipids, nor did consumption of the barley-derived β-glucan. The authors concluded that daily consumption of 5 g of oat β-glucan in a beverage improved glucose and lipid metabolism, while β-glucan from barley in the beverage matrix did not. It was noted that a dose–response effect of 5 g compared with 10 g of β-glucan was not shown in this study. Therefore, they concluded the level of β-glucan in a food product does not necessarily inform its effect on serum cholesterol concentrations.

In a study using men and women with mildly elevated blood cholesterol, Behall et al. (2004) investigated whether barley consumption reduced CVD risk factors on a similar scale with that of other sources of soluble fiber. In the study, 7 men (43±5 years), 9 postmenopausal women (50±3 years) and 9 premenopausal women (47±4 years) consumed American Heart Association Step 1 diets for 17 weeks. After an initial 2-week period, whole-grain foods containing barley β-glucan (0, 3, or 6 g/day) were included in the Step 1 diets for 5 weeks in a Latin square design. Subjects acted as their own controls, and fasting blood samples were collected 2 times/week. Triacylglycerol and HDL levels did not differ with the 3 amounts of dietary β-glucan. Total cholesterol was significantly lower with the diet at the 3 and 6 g/day β-glucan amount than with no β-glucan; the effect was most pronounced in the postmenopausal women and the men. The authors concluded that dietary changes including higher β-glucan intake, increased consumption of whole grains including barley, and decreased fat intake can reduce risk factors for CVD.

Shimizu and co-workers (2008) conducted a study in 44 hypercholesterolemic Japanese men evaluating whether consumption of a diet in which rice was replaced by high β-glucan barley would decrease LDL and total cholesterol, as well as the visceral fat area. In this double-blinded, randomized, placebo-controlled intervention study, participants (age 30-60 years) were randomly assigned to groups consuming either a 50:50 mixture of rice and pearl barley containing 7 g/day β-glucan or rice alone (control) for 12 weeks. Recruited participants regularly consumed pearled rice as a staple food source in more than 2 of 3 daily meals. Subjects consumed the diets, which were nearly identical in calories, for the entire 12 week period. Blood samples were taken and CT scans were performed before the study and every four weeks throughout the trial. Thirty-nine men completed the study. Barley intake was shown to significantly reduce LDL (153.4±16.4 vs 147.7±27.7 mg/dL) and total cholesterol (234.8±21.7 vs 223.8±33.9 mg/dL), as well as BMI, waist circumference and visceral fat. The authors concluded that consumption of pearl barley with a high β-glucan content reduces total- and LDL- cholesterol, as well as the visceral fat area.

In a 4-week crossover-designed experiment, 21 men with mildly elevated blood cholesterol (5.4-7.0 mmol/L), age 30-59 years, consumed comparable wheat and barley foods for 4 weeks (McIntosh et al., 1991). The authors examined the influence of two sources of dietary fiber on blood glucose and lipid concentrations. Wheat contained the largely insoluble cellulose and hemicellulose fiber (as a source of dietary fiber), while barley contained β-glucan. Both groups showed a significant increase in total dietary fiber, from a previous intake of 21-38 g/d. When compared to wheat, barley consumption was associated with a significant decrease in LDL-cholesterol (7%) and plasma total cholesterol (6%); significant changes did not occur in glucose and triglyceride concentrations. The authors concluded that barley dietary fiber is more effective than wheat dietary fiber at lowering blood cholesterol, particularly LDL-cholesterol, in men with high cholesterol levels.

Bourdon and co-workers (1999) studied the response of glucose, insulin, lipid, and cholecystokinin to 2 test meals containing β-glucan in 11 healthy American men (28.6 ± 2.0 years). One of the two meals was low in fiber (5.0 g) and the other had a high fiber

content (15.7 g). Two additional low-fiber (control) meals contained pasta prepared from wheat flour; the main one was a commercial preparation, and an additional one was prepared in-house. The high-fiber meals contained pasta made by replacing 40% of the wheat with 1 of 2 types of barley flour: flour enriched in β-glucan during processing or barley naturally high in β-glucan (Prowashonupana). Both types of high fiber meals contained approximately 5 g β-glucan. Each participant consumed each of the 3 test meals (two high-fiber, one commercial low-fiber), on 3 different days, 1–3 weeks apart in a randomized, crossover design. Five participants also consumed the noncommercial low-fiber control meal. Blood samples were taken at intervals from 30 to 360 min after the meal began. While both insulin and plasma glucose concentrations increased significantly after all meals, the insulin response was decreased following the meals containing barley. Cholecystokinin remained elevated for a longer time period after the barley-containing meals compared to the low-fiber meal. Four hours after the barley-containing meals, cholesterol concentrations fell below the fasting concentrations and were significantly lower than levels following consumption of the low-fiber meal. Cholesterol concentrations were not significantly altered after consumption of the low-fiber meal. The authors concluded that consumption of the barley-containing meals appeared to stimulate reverse cholesterol transport, which may be associated with barley's cholesterol-lowering effect. Also, carbohydrate was more slowly absorbed from the 2 high-fiber meals than the low-fiber meal.

Talati and coworkers (2009) performed a systematic literature review (through January 2008) to assess the association between consumption of β-glucan from barley and alterations in plasma lipids in hypercholesterolemic and healthy men and women. Barley studies were included if they were randomized, controlled trials that reported efficacy data for at least one lipid endpoint. Parallel and crossover trials were eligible; however, crossover studies required at least a 4-week washout period. The authors identified 8 trials (n = 391 participants) of 4-12 weeks in length, which evaluated barley's lipid-reducing effects and met the appropriate criteria. The β-glucan dose reported in the various studies was 3-10 g/day, with a median dose of 7 g/day. The β-glucan was present in various forms (e.g., barley bran flour, barley-containing beverages, pearled barley, barley concentrates). Barley consumption was found to significantly decrease triglycerides (weighted mean difference [WMD], –11.83 mg/dL; 95% CI, –20.12 to –3.55 mg/dL), total cholesterol (WMD, –13.38 mg/dL; 95% CI, –18.46 to –8.31 mg/dL), and LDL-cholesterol (WMD, –10.02 mg/dL; 95% CI, –14.03 to –6.00 mg/dL), but did not significantly affect HDL-cholesterol. The observed reduction in total- and LDL-cholesterol is consistent with a similar published meta-analysis of β-glucan derived from oats. Since barley and oats have similar β-glucan content (3.5%-5.9% of dry matter), this is reasonable. The authors concluded that β-glucan from barley appears to beneficially impact triglycerides, total- and LDL-cholesterol, but does not affect HDL-cholesterol. They further recommended that larger clinical trials be conducted to better evaluate the potential for a dose-response relationship with barley β-glucan. It was stated, "*Health practitioners should feel comfortable recommending barley β-glucan to their patients to help reduce total cholesterol and LDL cholesterol concentrations as recommended by the National Cholesterol Education Program guidelines.*"

Unlike the majority of the literature, Keogh and co-workers (2003) did not find an impact on blood cholesterol following β-glucan consumption. The authors conducted a randomized crossover intervention trial to determine whether consumption of a highly β-glucan enriched barley (75% by wt) would result in a clinically significant decrease in CVD risk in men with mildly elevated blood cholesterol (mean 4.0 ± 0.6 mmol LDL cholesterol/L). In this study, 18 men (38.8±10.1 years of age) were recruited on the basis of no history of CVD, mildly elevated LDL-cholesterol (>3.5 mmol/L), and no current treatment for hyperlipidemia. Participants were randomly assigned in this 2 x 4-wk, single-blind study to either the treatment arm [8.1–11.9 g /day β-glucan (scaled to body weight)] or the control arm (equally active dose of 6.5–9.2 g/day glucose). An oral-glucose-tolerance test was conducted on days 0 and 29; fasted blood samples were collected on days 0, 1, 7, 14, 21, 28, and 29. Following a 4-week washout period, the dietary regimens were crossed over. There was no significant change in total-, HDL-, or LDL- cholesterol, or in postprandial or fasting glucose when measured between treatments. The authors concluded that there was no evidence of a significant improvement in CVD risk, and the effect of β-glucan enriched barley on the lipid profile varied substantially between subjects. The authors hypothesized that the lack of observed effect may result from structural changes in β-glucan due to storage, freezing, or baking of the product during the intervention period, or from commercial processing of the barley into a highly enriched β-glucan product.

Studies of the Modulation of Blood Glucose and Insulin by Beta-Glucan

Tiwari and Cummins (2011) conducted a meta-analysis on epidemiologic studies to evaluate the relationship between oat and barley β-glucan consumption on blood glucose, cholesterol and triglyceride/triacylglycerol (TGL/TAG) levels. The authors identified 30 research articles (some with multiple dose levels) yielding 126 clinical studies. After β-glucan consumption, the overall analysis showed a significant change in blood glucose level (-2.58 mmol/L, 95% CI -3.22 to -1.84) with high heterogeneity between and across studies. There was a significant inverse relation in LDL-cholesterol (-0.66 mmol/L, 95% CI -0.96 to -0.36), total cholesterol (-0.60 mmol/L, 95% CI -0.85 to -0.34), and TGL/TAG (-0.04 mmol/L, 95% CI -0.15 to 0.07). However, an increase in HDL-cholesterol was noted (0.03 mmol/L, 95% CI -0.06 to 0.13). Dose-response modeling indicated that 3 g/day consumption of β-glucan derived from oats or barley was sufficient to decrease total cholesterol. The authors considered β-glucan's effect on blood glucose to be inconclusive, with high heterogeneity, and recommended additional clinical research studies with longer periods of intervention.

Using 32 healthy volunteers with normal body mass indices, Granfeldt and coworkers (2008) evaluated the effect of an extruded muesli product, which was based on oat bran rich in β-glucan, on post-meal glycemia and insulinemia. The study was performed in 2 series: Series 1 (19 subjects) test breakfast meals included 3 g β-glucan; Series 2 (13 subjects) test breakfast meals included 4 g β-glucan. Muesli was served in yogurt together with white bread. While 3 g β-glucan produced no significant impact on glycemic response (compared to a control meal without β-glucan and muesli), 4 g β-glucan significantly reduced both glucose and insulin responses. The authors concluded that 4 g

of oat-derived β-glucan appears to be a critical level for a significant decrease in insulin and glucose responses in healthy persons.

Using a Latin square design, Hallfrisch et al. (2003) conducted a study comparing insulin, glucose and glucagon responses following consumption of high-soluble β-glucan compounds from oats and barley. Eleven men and 11 women, 35–57 years, participated in the study. After consuming a prescribed diet for 3 days, on the third day of 5 periods, participants consumed 1 g/kg of carbohydrate as glucose or 0.66 g/kg pudding (mainly sucrose) and 0.33 g/kg as oat bran, oat or barley extract (Nu-trimX) or barley flour in a random design. Compared to the glucose solution, glucose responses to oats, barley, both extracts, and areas under the curve (AUC) were significantly decreased. The barley extract had the lowest insulin response. The authors stated that both oat and barley extracts retain the beneficial effects from the parent grains. While both oats and barley can help control plasma glucose response, high-soluble fiber barley is more effective than standard oats.

Liljeberg et al. (1996) performed a study with 9 healthy subjects (6 women and 3 men, 24-46 years). The purpose of the investigation was to evaluate the insulinemic and glycemic responses to porridge and bread products consisting of a barley genotype containing a high amount of β-glucan (Prowashonupana). The Prowashonupana contained 18 g/100 g dry weight β-glucan, which is approximately 4-fold higher than the levels in common barley or oats. In random order at 1-week intervals, at breakfast, subjects consumed products (porridge, bread or flatbread) made from oats, common barley or the barley containing high β-glucan levels. All high fiber barley products produced significantly lower postprandial insulin and glycemic responses than did the white bread reference (insulin and glycemic indices were 42-72%, and 57-72%, respectively). The most pronounced effect occurred for the flatbread made with 80% high-fiber barley flour. In contrast, common barley and oat porridges induced insulin and glucose responses similar to the reference bread, indicating that naturally occurring dietary fiber in these whole-meal flours has no effect on glucose tolerance. The authors concluded that pleasant tasting, "lente" products can be prepared from barley containing a high concentration of soluble dietary fiber. As the glycemic index of these products compares favorably with that of products made from common cereals, they could be used in diets for patients who are predisposed to metabolic disease, as well as those with hyperlipidemia and diabetes.

Nilsson et al. (2008b) evaluated the impact of 8 cereal-based bread evening meals (containing 50 g available starch), varying in content of indigestible carbohydrates and glycemic index, on glucose tolerance and related indices following a subsequent standardized breakfast. Study participants were 17 healthy volunteers (6 women and 11 men, 22-32 years of age) with normal BMI (22.5±2.1 kg/m^2); one male and one female did not complete the study. The participants consumed the test meals approximately once per week in random order. One of the meals contained bread from a barley variety with elevated β-glucan levels (14% dry basis, mutant 13, Svalöf Weibull); the other test meals contained various types of wheat or barley. At breakfast, blood samples were collected for 15- and 3-minute intervals over 3 hours for measurement of blood glucose, serum

insulin, and other clinical parameters, and satiety was subjectively rated after breakfast. At the subsequent breakfast, glucose tolerance was improved after consuming evening meals with barley kernel-based bread (including the β-glucan-rich genotype) or white wheat flour bread enriched with resistant starch and barley fiber, compared to non-enriched white wheat bread. At breakfast, glucose response and colonic fermentation were inversely correlated (r = -0.25). Breath hydrogen (marker of colonic fermentation) correlated inversely with gastric emptying rate (r = -0.23) and positively with satiety (r = 0.27). The authors stated that the high β-glucan bread produced a low and prolonged net increment in blood glucose and a higher feeling of satiety, likely due to lowered gastric emptying rate. The authors concluded that the constitution of indigestible carbohydrates in the evening meal may impact glycemic excursions and related metabolic risk variables at breakfast through a mechanism involving colonic fermentation. These results provide evidence of a link between gut microbial metabolism and key factors involved in insulin resistance.

In a randomized crossover study of 17 normoglycemic, obese women at increased risk for insulin resistance, Kim et al. (2009) investigated the linearity of reduced glucose and insulin responses after consumption of whole grains containing soluble fiber. After consuming controlled diets for 2 days, the participants (51.6±2.1 years, BMI 33.2±0.8) consumed 5 hot breakfast cereal test meals containing barley and/or wheat containing varying amounts of β-glucan (0, 2.5, 5, 7.5 and 10 g). Each test day was separated by a washout period of 7 days. Blood samples were collected before and 30, 60, 120 and 180 min after test meal consumption. Consumption of 10 g β-glucan delayed the rate of glucose response and significantly decreased peak glucose response at 30 min. β-glucan content did not impact the AUC for 2-hour postprandial glycemic response. However, both AUC and peak insulin responses were significantly affected by β-glucan concentration in an inverse linear relationship. The authors concluded that in obese women who are at risk for insulin resistance, acute consumption of 10 g β-glucan can induce beneficial effects on postprandial insulin responses. The authors hypothesized that this effect may be mediated by changes in gut hormones.

Keogh and coworkers (2007) conducted a randomized-single-blinded crossover study of 14 lean, healthy women (28.6±8.3 years, BMI 22.8±2.3 kg/m^2) to investigate the impact of barley flour vs. white wheat flour on the subsequent food intake, thermic effect of food (TEF), and metabolic indices. The barley (barley cultivar, Hordeum Vulgare var Himalaya 292) or wheat flour was incorporated into breakfast and lunch. β-glucan concentrations varied between 3.2 and 4.0 g/serving for the barley items and were 0.5 g/serving for all wheat items. Each test day was separated by a 7-day washout period. Blood samples were collected 6 hours after breakfast, then at 30, 60, 120 and 180 min after beginning lunch. The results showed that *ad libitum* food intake over the next 10 hours was decreased by 23% following the wheat-containing meals compared to the barley-containing meals. TEF was 5% for both test lunches. Mean AUC of insulin following consumption of the wheat-containing meals was 32% greater than the barley-containing meals (78.1±35.3 vs 52.8±24.7 mmol/L/h). AUC for glycemic response for wheat-containing meals was 22% higher than for the barley-containing meals (4.68±1.67 mmol/L/h, 3.67±1.91 mmol/L/h). The authors concluded that meals containing increased

amylose and soluble fiber did not reduce spontaneous food intake, but rather were associated with higher energy intakes, despite lowering glucose and insulin levels.

Studies of Immune-Modulating Effects of Beta-Glucan

Rieder and Samuelsen (2012) state that β-glucans are known for having immune-modulating properties and have been shown to protect against viral, bacterial, and parasitic infections in mice. The authors cite a number of studies in mice discussing immunological effects of oat β-glucans; effects include increased resistance to herpes virus infection, increased cytokine secretion spleen cells and macrophages, increased resistance to *Eimeria vermiformis* and *Stapyhlococcus aureus* infection, and increase in respiratory burst activity of neutrophils. Other effects include diminished spread of lung tumor metastasis, NF-κB activation of intestinal epithelial cells and leukocytes. However, human studies of oat β-glucan exposure did not cause any changes in various immunological parameters, including leukocyte activity, reported upper respiratory tract infections, cytokine production, or C-reactive protein level (Rieder and Samuelsen, 2012).

Since *in vitro* β-glucan can increase tumor cytotoxicity via iC3b receptors on leukocytes, Cheung and Modak (2002) studied whether (1→3),(1→4)-D-β-glucan could synergize with anti-GD2 monoclonal antibody (MoAb) 3F8 (mouse IgG3) in treating human neuroblastoma xenografts. In the study, nude, athymic mice with neuroblastoma xenografts were treated daily with β-glucan, i.p. or p.o. administration. The treatments occurred with or without i.v. MoAb administration twice a week, for 22–29 days. Body weights and serial tumor volumes were measured. The results showed that an antitumor effect was seen at ≥40 μg of β-glucan dose, i.v. or p.o., in all human neuroblastoma lines. β-glucan with 3F8 yielded near-complete disease stabilization/tumor regression, while β-glucan or 3F8 alone did not significantly impact tumor growth. While <3% of controls remained progression free, 18% percent of the mice with LAN-1 cell line and 47% of those NMB7 cell line did not show progression. No toxicities were observed in animals treated with either β-glucan alone or 3F8 plus β-glucan (4–4,000 μg/dose). It is hypothesized that β-glucan plus complement activation may increase B-cell response to tumor cells, or innate immunity may be involved following β-glucan leukocyte activation. The authors concluded that p.o. β-glucan synergized with antitumor IgM and IgG MoAb in this *in vivo* study. Since β-glucan was well tolerated and inexpensive, it could be potentially valuable in chemotherapy (Cheung and Modak, 2002).

Additional Protective Effects of Beta-Glucan

Nilsson et al. (2008a) administered 40 g β-glucan-enriched oat bran per day, in 4 slices of bread to 25 healthy subjects (age 24± 1.3 years) for 12 weeks. The objective of the study was to determine how the colonic concentration of carboxylic acids in healthy subjects is influenced by dietary supplementation with oat bran. Carboxylic acids, particularly butyric acid, are believed to counteract colonic diseases, such as colon cancer and ulcerative colitis. Oat bran increased the fecal carboxylic acid levels after 8 weeks, which also indicated an increased concentration in the distal colon. Fecal concentrations of

butyric, acetic, isobutyric, isovaleric and propionic acids were significantly higher after 8 weeks on the oat bran diet as compared with initial values, but lactic acid concentrations were lower. After 12 weeks, isobutyric, acetic and propionic acid concentrations were still higher and lactic acid levels were lower. Inter-individual variation was high, whereas intra-individual variation was low. The authors concluded that oat bran may have the potential to protect against colonic diseases.

Tolerance Studies in Human Volunteers

As discussed above, in multiple studies evaluating the potential benefits of β-glucan products, human volunteers have consumed these products under controlled conditions. Toxic effects did not occur in any of the studies. In 2 recent meta-analyses (Tiwari and Cummins, 2011; Othman et al., 2011), and 1 earlier one (Ripsin et al., 1992), safety concerns were not reported following consumption of oat β-glucan.

In an 11-week controlled crossover study by Hallfrisch and Behall (1997), 17 women and 7 men (37-61 years) consumed diets in which the fat content of foods was reduced by Oatrim addition. The Oatrim contained either a low (1%) or high (10%) level of soluble β-glucan. While a significantly longer adaptation period and gastrointestinal symptoms (5 vs. 13 days) were more often reported for the meals containing the higher β-glucan level, the effects were not serious enough for any of the subjects to withdraw or refuse to consume any of the foods. In healthy men with elevated blood cholesterol levels, Beer et al. (1995) reported that the participants experienced mild, transient GI effects after consumption of 9 g/day oat β-glucan in oat gum instant whip. In their study investigating whether barley consumption reduced CVD risk factors on a similar scale with that of other sources of soluble fiber, Behall et al. (2004) administered American Heart Association Step 1 diets for 17 weeks with whole-grain foods containing barley β-glucan (0, 3, or 6 g/day). Persons on the high β-glucan diet indicated they were experiencing bloating and flatulence.

Interaction with Nutrient Absorption

Due to their soluble fiber content, oats are known for retarding absorption of nutrients and their effects on satiety, as well as a deterrent for various GI disorders. Oat β-glucan lowers the rate of glucose absorption and delays intestinal absorption of carbohydrates, all beneficial effects (Daou and Zhang, 2012).

Cargill (FDA, 2011) stated that β-glucan does not complex with metal ions, therefore it is not anticipated to impair absorption of essential minerals in the small intestine. Upon review of the literature, Cargill (FDA, 2011) concluded that dietary fiber, at recommended intake levels, does not adversely affect vitamin and mineral absorption of the average consumer. According to the American Dietetic Association (ADA, 2008):

> *Potential negative effects of excessive dietary fiber include reduced absorption of vitamins, minerals, proteins, and energy. It is unlikely that healthy adults who consume dietary fiber in amounts within the recommended ranges will have problems with nutrient absorption; however, high dietary fiber intakes may not be appropriate*

for children and older adults because so little research has been conducted in these populations.

Allergenicity

Children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2013).

Allergy manifestation resulting from consumption of oats and oat products has been debated. It has been alleged that oats may cause adverse effects in individuals with celiac disease. As a result, use of oats in gluten-free diets was not allowed. Evidence from more recent reports indicates that oats are safe for consumption by most individuals with celiac disease (Rashid et al., 2007). Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. It is recognized that commercially available oats are variably contaminated with gluten-containing grains that can occur on the farms, during the growing cycle or during storage, cleaning, transportation or processing.

Rashid et al. (2007) reported that in past years, oats were not allowed in a gluten-free diet and were considered to be averse to persons with celiac disease. However, based on recent data, pure oats, uncontaminated with other gluten-containing grains, if consumed in limited amounts, are safe for most of those with celiac disease. For children, up to 25 g/day (1/4 cup) and for adults, up to 70 g/day (1/2 to 3/4 cup) is a safe consumption rate (Rashid et al., 2007). With the current labeling of gluten-free foods, these are helpful guidelines for consumers with celiac disease to use as a reference. Health Canada supports the position that oats can be part of a gluten-free diet, indicating that persons with celiac disease can tolerate some amounts of pure oats (uncontaminated with other cereal grains such as wheat, barley and rye). In fact, pure oats may be beneficial to persons with celiac disease, as its palatability may increase patients' compliance with a gluten-free diet (Health Canada, 2007).

Oat consumption by celiac disease patients is not widely recommended in the U.S. due to concerns of potential contamination of commercial oats (Kupper, 2005; American Celiac Society, 2014). According to the National Foundation for Celiac Awareness (NFCA, 2014), although oats do not contain gluten, a small percentage of persons with celiac disease react to pure, uncontaminated oats. Further, most mills that process oats also manufacture grains which contain gluten, making cross contamination likely. However, up to 50 g/day of dry, gluten-free oats is considered safe (NFCA, 2014).

The potential allergenicity of β-glucan in itself was researched in the available literature, but no relevant information was located. Natural sources of β-glucan concentrates, such as barley, have been safely consumed for decades. β-glucan is not listed among FDA's list of the 8 major food allergens (FDA, 2010). The lack of available information and

absence from FDA's list leads to the conclusion that allergic reactions to β-glucan itself are not of concern.

C. Safety Data Summary

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2013). Numerous food products containing oats are currently marketed in the U.S. and around world. Oat fiber has become a desirable ingredient for addition to a variety of food products as a source of dietary fiber.

Oat β-glucan is found in the cell walls of oat kernels. Beside oats, β-glucan is consumed from other cereals and edible plants such as barley, rye, and wheat. Oat-derived β-glucan concentrates (e.g., Oatrim with a β glucan content of up to 10% and OatVantage™ with 54% β-glucan) are marketed in the United States and have GRAS status (FDA, 2011; FDA, 2013). Quaker Oats self-determined the GRAS status of Oatrim in 1992 (FDA, 2011). As described in GRAS Notification No. 437 (FDA, 2012), the GRAS status of Oatrim was supported by several factors including: 1) Oatrim's similarity to oat starch and maltodextrin (food ingredients with a known safety use profile), 2) the enzymatic manufacturing process was analogous to the biological digestion of starch by humans, and 3) short-term toxicity studies and safety evaluations of Oatrim's constituents did not reveal any areas of concern (FDA, 2011; FDA, 2013). OatVantage™ (54% β-glucan content) has similarly been on the market for 10+ years and no safety concerns have been reported.

Numerous studies have been conducted and published in support of the evaluation of the safety of barley β-glucan, including *in vitro* and *in vivo* animal studies as well as clinical studies in humans. While there is a lack of published preclinical safety studies on oat β-glucan, products containing oat β-glucan concentrates have been employed in numerous clinical trials. Other than mild, transient gastrointestinal (GI) effects such as flatulence and abdominal discomfort, no significant adverse effects were noted. It should be noted that these GI effects commonly occur following a shift from a low- to high-fiber diet (IOM, 2005). Updated literature searches covering the period of 2010 – present have revealed no recent studies that report safety concerns.

Epidemiological studies and clinical trials have consistently revealed that fiber-rich diets are associated with significant reductions in cardiovascular disease risk and other health benefits. The intended uses of PromOat® have the potential to increase the dietary fiber intakes among the US population. The Institute of Medicine (2005) reviewed the possible effect of cereal fiber on mineral absorption (e.g., iron, zinc, calcium, magnesium) and determined that dietary fiber, as part of a balanced diet, has not been found to adversely affect mineral status in healthy people at recommended intake levels.

Children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2013).

Allergy manifestation resulting from consumption of oats and oat products has been the subject of debate. It has been alleged that oats may cause adverse effects in individuals with celiac disease. As a result, use of oats in a gluten-free diets was not allowed. Evidence from more recent reports indicates that oats are safe for consumption by most individuals with celiac disease (Rashid et al., 2007).

For instance, Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. Rashid et al. (2007) reported that in past years, oats were not allowed in a gluten-free diet and were considered to be averse to persons with celiac disease. However, based on recent data, pure oats, uncontaminated with other gluten-containing grains, if consumed in limited amounts, are safe for most of those with celiac disease. Health Canada supported this position, indicating that persons with celiac disease can tolerate some amounts of pure oats (uncontaminated with other cereal grains such as wheat, barley and rye). In fact, pure oats may be beneficial to persons with celiac disease, as its palatability may increase patients' compliance with a gluten-free diet (Health Canada, 2007).

The potential allergenicity of β-glucan itself was researched in the available literature, but no relevant information was located. Natural sources of β-glucan concentrates, such as barley, have been safely consumed for decades. β-glucan is not listed among FDA's list of the 8 major food allergens (FDA, 2010). The lack of available information and absence from FDA's allergen list leads to the conclusion that allergic reactions to β-glucan itself are not of concern.

6.0 Basis for the GRAS Determination

A. Introduction

The regulatory framework for determining whether a substance can be considered generally recognized as safe (GRAS) in accordance with section 201(s) (21 U.S.C. § 321(s)) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et. Seq.) ("the Act"), is set forth at 21 CFR 170.30, which states:

> General recognition of safety may be based only on the view of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.
>
> General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. General recognition of safety through scientific procedures shall ordinarily be based upon published studies, which may be corroborated by unpublished studies and other data and information.

These criteria are applied in the analysis below to determine whether the use of an oat-derived β-glucan for use in food for human consumption is GRAS based upon scientific procedures. All data used in this GRAS determination are publicly available and generally known, and therefore meet the "general recognition" standard under the FD&C Act.

B. Safety Determination

The subject of this GRAS determination is the use of oat-derived β-glucan for use as a source of dietary fiber for general addition to all foods except infant formula and meat and poultry products. There is a long history of the safe use of oats and products derived from oats such as oat β-glucan concentrates. Furthermore, other natural sources of β-glucan concentrates, such as barley, have been safely consumed for decades. While there is a noted lack of published safety studies of oat β-glucan concentrates, the safety section describes numerous animal and human safety studies of barley β-glucan which is similar to oat β-glucan, as both contain polysaccharides of unbranched, linear, mixed-linkage (1-3)(1-4)-β-D-glucan.

The focus of this GRAS self-determination is for an identical general food use of oat-

derived β-glucan (excluding infant formula and meat and poultry) as current barley- and oat-derived β-glucan products as described in GRN 207, 344, and 437 (FDA, 2006; FDA, 2011; FDA, 2013). Cargill, in GRAS Notification 344, estimated the combined average intake of barley betafiber by consumers from all uses of barley betafiber (i.e., general food use and meat and poultry) would be 12.4 g/person/day (8.7 g β-glucan/person/day). The 90th percentile intake was estimated to be 23.5 g/person/day (16.5 g β-glucan/person/day). Cargill stated that barley betafiber would be added to food at levels of 4.3 g/serving, resulting in approximately 3 g of β- glucan/serving. Given the lower level of β-glucan (approximately 35%) in Tate & Lyle's PromOat® product, the estimated intake of β-glucan from the proposed uses of Tate & Lyle's product will be lower by approximately 50% (i.e., 4.35 and 8.25 g β-glucan/person/day for the mean and 90th percentile, respectively). While Tate & Lyle's PromOat® product could be added at a higher per serving level, the use of oat β-glucan in this manner is considered to be self-limiting for technological reasons such as product texture and/or flavor profile. In addition, since use in infant formula, medical foods, and meat and poultry are not being considered as part of this GRAS Notification, the resulting estimated intake will be less than the current GRAS oat- and barley-derived β glucan products that were the subject of GRN Nos. 207, 344, and 437. In summary, the proposed uses of PromOat® will not result in an increase in the overall consumption of β-glucan, but simply provide an alternative source of β-glucan for use in food.

Numerous studies have been conducted and published in support of the evaluation of the safety of barley β-glucan, including *in vitro* and *in vivo* animal studies as well as clinical studies in humans. While there is a lack of published preclinical safety studies on oat β-glucan, products containing oat β-glucan concentrates have been employed in numerous clinical trials. Other than mild, transient gastrointestinal (GI) effects such as flatulence and abdominal discomfort, no significant adverse effects were noted. It should be noted that these GI effects commonly occur following a shift from a low- to high-fiber diet. Evaluation of the possible effects of oats, cereal fiber and/or β-glucan on mineral absorption and allergenicity have also been considered by U.S. FDA and EFSA and found not to present a significant safety concern as consumed as part of the normal diet.

C. General Recognition of the Safety of Oat Beta-Glucan

The intended use of oat β-glucan has been determined to be safe through scientific procedures as set forth in 21 CFR§170.3(b), thus satisfying the so-called "technical" element of the GRAS determination.

The oat β-glucan that is the subject of this notification (PromOat® Beta Glucan) is produced from the starting material oat bran. The oat β-glucan product is manufactured consistent with current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110). The raw materials used in the manufacturing process are food grade and/or approved for use as processing aids in food. No chemical processing aids are employed in the manufacturing process. The oat β-glucan product containing approximately 35% β-glucan has been characterized and meets the food grade specifications found in Table 1.

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats (FDA, 2013). Numerous food products containing oats are currently marketed in the U.S. and around world. Oat fiber has become a desirable ingredient for addition to a variety of food products as a source of dietary fiber.

Epidemiological studies and clinical trials have consistently revealed that fiber-rich diets are associated with significant reductions in cardiovascular disease risk. While there is no established dietary reference value (DRV) for soluble fiber, the amount of soluble fiber in a typical mixed diet is one-fourth to one-third of the total dietary fiber intake (ADA, 2002; FDA, 2013). The intended uses of PromOat® (oat-derived β-glucan) will provide an alternative to other dietary sources of β-glucan as part of the total dietary fiber intakes among the U.S. population.

Oat β-glucan is found in the cell walls of oat kernels. Besides oats, β-glucan is consumed from other cereals and edible plants such as barley, rye, and wheat. Oat-derived β-glucan concentrates (e.g., Oatrim with a β glucan content of up to 10% and OatVantage™ with 54% β-glucan) are marketed in the United States and have GRAS status (FDA, 2011; FDA, 2013).

To date, FDA has reviewed two GRAS Notifications of β-glucan from barley (FDA, 2006; FDA, 2011) and one from oats (FDA, 2013). Extensive published information and data on β-glucan were submitted. All of the GRAS notifications received "no questions" letters from the FDA. Tate & Lyle considers the information and study data described in these cited notifications as directly applicable to this notification. Furthermore, β-glucan derived from oats or barley contains polysaccharides of unbranched, linear, mixed-linkage (1-3), (1-4)-β-D-glucan, and from a physiological perspective there is virtually no difference. Thus, from a safety perspective, the available studies of barley β-glucan and the studies described in GRNs 207, 344, and 437 are applicable to the safety assessment of oat β-glucan. No recent studies raising any new safety concerns have appeared in the published literature subsequent to these evaluations, particularly the most recent GRAS notice GRN 437.

Given that oat β-glucan meets the proposed specifications for the use of β-glucan as a food ingredient for human consumption, the safe use of oat β-glucan is justified by scientific procedures. In addition, the publicly available scientific literature is sufficient to support the safety and GRAS status of the proposed oat β-glucan product.

Numerous studies have been conducted and published in support of the evaluation of the safety of β-glucan, including *in vitro* and *in vivo* animal studies as well as clinical studies in humans and are described herein. Therefore, since this safety evaluation was based on generally available and widely accepted data and information, it also satisfies the so-called "common knowledge" element of a GRAS determination.

Determination of the safety and GRAS status of oat β-glucan that is the subject of this self-determination has been made through the deliberations of an Expert Panel convened by Tate & Lyle and comprised of Michael Carakostas, DVM, Ph.D., Carol A. Knight, Ph.D., and Stanley M. Tarka, Jr., Ph.D. These individuals are qualified by scientific training and experience to evaluate the safety of substances intended to be added to foods. They have critically reviewed and evaluated the publicly available information summarized in this document and have individually and collectively concluded that oat-derived β-glucan, produced consistent with Good Manufacturing Practice and meeting the specifications described herein, is safe under its intended conditions of use. The Panel further unanimously concludes that these uses of oat β-glucan are GRAS based on scientific procedures, and that other experts qualified to assess the safety of foods and food additives would concur with these conclusions. The Panel's GRAS opinion is included as Exhibit 1 to this document.

It is also Tate & Lyle's opinion that other qualified scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Tate & Lyle has concluded that oat β-glucan is GRAS under the intended conditions of use on the basis of scientific procedures; and therefore, it is excluded from the definition of a food additive and may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

Tate & Lyle is not aware of any information that would be inconsistent with a finding that the proposed use of oat β-glucan in food for human consumption meeting appropriate specifications and used according to Good Manufacturing Practice, is GRAS. Recent reviews of the scientific literature revealed no potential adverse health concerns.

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8.0 Appendices

44

Appendix A. Certificates of Analysis – Characterization

TATE & LYLE

CERTIFICATE OF ANALYSIS

Product: **100 015 PromOat Betaglucan**

Batch no: (b)

Prod. Date: **24-06-2013**

Best before: **23-06-2015**

Chemical analysis	**Result**	**Unit**
Average value		
Beta Glucan	34	%
Dry matter	94,7	%

Bacteriological analysis

Total plate count	<500	cfu/g
Enterobacteriaceae	<10	cfu/g
Staff. Aureus	<20	cfu/g
Yeast	<60	cfu/g
Moulds	<80	cfu/g
Salmonella	Neg/25g.	
E-coli	Negative	

Tate&Lyle Sweden AB
03-09-2014

(b) (6)

Ingbritt Johansson
Quality Manager

TATE & LYLE

CERTIFICATE OF ANALYSIS

Product: **100 015 PromOat Betaglucan**

Batch no: [redacted]
(6)

Prod. Date: **30-10-2014**

Best before: **29-10-2015**

Chemical analysis	**Result**	**Unit**
Average value		
Beta Glucan	35	%
Dry matter	94,3	%

Bacteriological analysis

Total plate count	<600	cfu/g
Enterobacteriaceae	<10	cfu/g
Staff. Aureus	<20	cfu/g
Yeast	<20	cfu/g
Moulds	<80	cfu/g
Salmonella	Neg/25g.	
E-coli	Negative	

Tate&Lyle Sweden AB
03-09-2014

(b) (6)
[redacted]

Ingbritt Johansson
Quality Manager

TATE & LYLE

CERTIFICATE OF ANALYSIS

Product: **100 015 PromOat Betaglucan**

Batch no: [redacted]
(6)

Prod. Date: **11-03-2014**

Best before: **10-03-2016**

Chemical analysis	**Result**	**Unit**
Average value		
Beta Glucan	34	%
Dry matter	94	%

Bacteriological analysis

Total plate count	<100	cfu/g
Enterobacteriaceae	<10	cfu/g
Staff. Aureus	<20	cfu/g
Yeast	<20	cfu/g
Moulds	<20	cfu/g
Salmonella	Neg/25g.	
E-coli	Negative	

Tate&Lyle Sweden AB
03-09-2014

[redacted]

Ingbritt Johansson
Quality Manager

eurofins

Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

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AR-14-LW-018537-01

EUSELI-00064747

Client code:: LW9901581

ANALYTICAL REPORT

Sample code: (b) (6)
Client Sample: PromOat 1411
Received: 2014-04-28
Report finished: 2014-05-06
Start of analysis 2014-04-28

	Analysis	Result:	MRL	Unit	Uncert.	Method	Lab
LW00V	Fat acc. Soxtec	0.33		g/100 g	± 30%		EUSELI
SL412	Sodium (Na)	250		mg/kg	± 25%	NMKL No 139 1991 mod	EUSELI2
SL408	Calcium (Ca)	91		mg/kg	± 10%	NMKL No 139 1991 mod	EUSELI2
SL411	Magnesium (Mg)	370		mg/kg	± 10%	NMKL No 139 1991 mod	EUSELI2
SL413	Iron (Fe)	< 2.0		mg/kg	± 30%	NMKL No 139 1991 mod	EUSELI2
SL410	Potassium (K)	7400		mg/kg	± 15%	NMKL No 139 1991 mod	EUSELI2
SL409	Phosphorus (P)	2800		mg/kg	± 10%	NMKL No 139 1991 mod	EUSELI2
SL415	Zinc (Zn)	1.5		mg/kg	± 20%	NMKL No 139 1991 mod	EUSELI2
SL405	Aluminium (Al)	< 5.0		mg/kg	± 30%	NMKL No 161 1998 mod	EUSELI2
SL403	Lead (Pb)	< 0.020		mg/kg	± 20%	NMKL No 161 1998 mod	EUSELI2
SL404	Cadmium (Cd)	< 0.010		mg/kg	± 20%	NMKL No 161 1998 mod	EUSELI2
SL402	Arsenic (As)	<0.050		mg/kg	± 35%	NMKL No 161 1998 mod	EUSELI2
SL399	Mercury (Hg)	< 0.020		mg/kg	± 30%	EN 16277:2012	EUSELI2
JJ006	Aflatoxin B1	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin B2	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin G1	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin G2	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
LW020	Ochratoxin	0.14		µg/kg	± 30%	NMKL 143	EUSELI
LW03Z	Deoxynivalenol (Vomitoxin)	58		µg/kg	± 25%	In house method (210)	EUSELI

Uncert: Measurement uncertainty

Symbol description:
* : (Not part of the accreditation)
Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

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LW03X	HT-2 Toxin	<10	µg/kg	± 30%	In house method (210)	*EUSELI*
LW03Y	T-2 Toxin	<10	µg/kg	± 30%	In house method (210)	*EUSELI*
LW041	Zearalenone (ZON)	<10	µg/kg	± 35%	In house method (210)	*EUSELI*
MJ011	Starch and sugar	42	g/100 g		Internal method	*EUNOTR2*
SLB89	Sulphur total (S)	1600	mg/kg	± 20%	NMKL No 161 1998 mod	*EUSELI2*

LP130: No pesticide residue detected (SLV K1-f4-m016.1).

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

Test was performed by

EUHAWE3	Eurofins WEJ Contaminants GmbH (Hamburg)
EUNOTR2	Eurofins Food & Agro Testing Norway AS (Skansen), Trondheim
EUSELI	Eurofins Food & Agro Testing Sweden AB, Lidköping
EUSELI2	Eurofins Environment Sweden, Lidköping

Uncert: Measurement uncertainty

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Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

Eurofins Food & Agro Testing Sweden AB
Box 887
Sjöhagsg. 3
SE-53119 Lidköping
www.eurofins.se

Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

AR-13-LW-028445-01

EUSELI-00046392

Client code: LW9901581

ANALYTICAL REPORT

Sample code:	**525-2013-07170148**
Client Sample:	Soluble Oat Fibre, Batch: 1326
Received:	2013-07-17
Report finished:	2013-07-30
Start of analysis	2013-07-22

	Analysis	Result:	MRL	Unit	Uncert.	Method	Lab
LW00V	Fat acc. Soxtec	**0.42**		g/100 g	± 30%		*EUSELI*
SL412	Sodium (Na)	**280**		mg/kg	± 25%	NMKL No 139 1991 mod	*EUSELI2*
SL408	Calcium (Ca)	**83**		mg/kg	± 10%	NMKL No 139 1991 mod	*EUSELI2*
SL411	Magnesium (Mg)	**380**		mg/kg	± 10%	NMKL No 139 1991 mod	*EUSELI2*
SL413	Iron (Fe)	**3.2**		mg/kg	± 30%	NMKL No 139 1991 mod	*EUSELI2*
SL409	Phosphorus (P)	**3100**		mg/kg	± 10%	NMKL No 139 1991 mod	*EUSELI2*
SL405	Aluminium (Al)	**<5.0**		mg/kg	± 30%	NMKL No 161 1998 mod	*EUSELI2*
SL403	Lead (Pb)	**<0.020**		mg/kg	± 20%	NMKL No 161 1998 mod	*EUSELI2*
SL404	Cadmium (Cd)	**<0.010**		mg/kg	± 20%	NMKL No 161 1998 mod	*EUSELI2*
SL402	Arsenic (As)	**<0.050**		mg/kg	± 35%	NMKL No 161 1998 mod	*EUSELI2*
SL399	Mercury (Hg)	**< 0.020**		mg/kg	± 30%	EN 16277:2012	*EUSELI2*
JJ006	Aflatoxin B1	**<0.1**		µg/kg		internal method based on EN 14123	*EUHAWE3*
JJ006	Aflatoxin B2	**<0.1**		µg/kg		internal method based on EN 14123	*EUHAWE3*
JJ006	Aflatoxin G1	**<0.1**		µg/kg		internal method based on EN 14123	*EUHAWE3*
JJ006	Aflatoxin G2	**<0.1**		µg/kg		internal method based on EN 14123	*EUHAWE3*
LW020	Ochratoxin	**<0.10**		µg/kg	± 30%	NMKL 143	*EUSELI*
LW03Z	Deoxynivalenol (Vomitoxin)	**200**		µg/kg	± 25%	In house method (210)	*EUSELI*
LW03X	HT-2 Toxin	**<10**		µg/kg	± 30%	In house method (210)	*EUSELI*
LW03Y	T-2 Toxin	**<10**		µg/kg	± 30%	In house method (210)	*EUSELI*
LW041	Zearalenone (ZON)	**<10**		µg/kg	± 25%	In house method (210)	*EUSELI*

Uncert: Measurement uncertainty

Symbol description:
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Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

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AR-13-LW-028445-01

EUSELI-00046392

LP130	Dimethylaminosulphotoluidide (DMST)	**0.014**		mg/kg		SLV K1-f4-m016.1	*EUSELI*
LP130	Diphenylamine	**0.014**	0.05	mg/kg		SLV K1-f4-m016.1	*EUSELI*
MJ011	Starch and sugar	**44**		g/100 g		AOAC 996.12	*EUNOTR2*
SLB89	Sulphur total (S)	**1400**		mg/kg	± 20%	NMKL No 161 1998 mod	*EUSELI2*

LP130: No other pesticide residues detected (SLV K1-f4-m016.1).

Sample conclusion:

Pesticide residues have a measurement uncertainty at an interval of 30-60%.

Ulrica Svensson, ASM

This test report has been created electronically and has been verified and authorised.

Test was performed by

EUHAWE3	Eurofins WEJ Contaminants GmbH (Hamburg)
EUNOTR2	Eurofins Food & Agro Testing Norway AS (Skansen), Trondheim
EUSELI	Eurofins Food & Agro Testing Sweden AB, Lidköping
EUSELI2	Eurofins Environment Sweden, Lidköping

Uncert: Measurement uncertainty

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Rapport utfärdad av ackrediterat laboratorium

Report issued by Accredited Laboratory

Eurofins Food & Agro Testing Sweden AB
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Tlf: +46 10 490 8310

Tate&Lyle Sweden AB
Ingbritt Johansson
Älvåsvägen 1
610 20 KIMSTAD

AR-13-LW-047866-01

EUSELI-00054839

Client code: LW9901581

ANALYTICAL REPORT

Sample code: (b) (6)
Client Sample: Soluble Oat Fibre, Batch 1344-1
Received: 2013-12-03
Report finished: 2014-01-03
Start of analysis: 2013-12-04

	Analysis	Result	MRL	Unit	Uncert.	Method	Lab
LW00V	Fat acc. Soxtec	0.71		g/100 g	± 10%		EUSELI
SL412	Sodium (Na)	21		mg/100 g	± 25%	NMKL No 139 1991 mod	EUSELI2
SL406	Calcium (Ca)	8.0		mg/100 g	± 10%	NMKL No 139 1991 mod	EUSELI2
SL411	Magnesium (Mg)	36		mg/100 g	± 10%	NMKL No 139 1991 mod	EUSELI2
SL413	Iron (Fe)	0.20		mg/100 g	± 30%	NMKL No 139 1991 mod	EUSELI2
SL410	Potassium (K)	700		mg/100 g	± 15%	NMKL No 139 1991 mod	EUSELI2
SL409	Phosphorus (P)	300		mg/100 g	± 10%	NMKL No 139 1991 mod	EUSELI2
SL415	Zinc (Zn)	0.22		mg/100 g	± 20%	NMKL No 139 1991 mod	EUSELI2
SL405	Aluminium (Al)	<5.0		mg/kg	± 30%	NMKL No 161 1998 mod	EUSELI2
SL403	Lead (Pb)	< 0.020		mg/kg	± 20%	NMKL No 161 1998 mod	EUSELI2
SL404	Cadmium (Cd)	< 0.010		mg/kg	± 20%	NMKL No 161 1998 mod	EUSELI2
SL402	Arsenic (As)	< 0.050		mg/kg	± 35%	NMKL No 161 1998 mod	EUSELI2
SL399	Mercury (Hg)	< 0.020		mg/kg	± 30%	EN 16277:2012	EUSELI2
JJ006	Aflatoxin B1	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin B2	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin G1	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
JJ006	Aflatoxin G2	<0.1		µg/kg		internal method based on EN 14123	EUHAWE3
LW020	Ochratoxin	<0.10		µg/kg	± 30%	NMKL 143	EUSELI
LW03Z	Deoxynivalenol (Vomitoxin)	82		µg/kg	± 25%	In house method (210)	EUSELI

Uncert: Measurement uncertainty

Symbol description:
* : (Not part of the accreditation)
Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

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AR-13-LW-047866-01

EUSELI-00054839

LW03X	HT-2 Toxin	<10	µg/kg	± 30%	In house method (210)	EUSELI
LW03Y	T-2 Toxin	<10	µg/kg	± 30%	In house method (210)	EUSELI
LW041	Zearalenone (ZON)	<10	µg/kg	± 35%	In house method (210)	EUSELI
MJ011	Starch and sugar	44	%		AOAC 996.12	EUNOTR2
SL589	Sulphur total (S)	140	mg/100 g	± 20%	NMKL No 161 1998 mod	EUSELI2

LP130: No pesticide residue detected (SLV K1-I4-m016.1).

Report comments:

Pesticide residues have a measurement uncertainty at an interval of 30-60%.

Per-Olov Södergren, ASM

This test report has been created electronically and has been verified and authorised.

Test was performed by

EUHAWE3	Eurofins WEJ Contaminants GmbH (Hamburg)
EUNOTR2	Eurofins Food & Agro Testing Norway AS (Skansen), Trondheim
EUSELI	Eurofins Food & Agro Testing Sweden AB, Lidköping
EUSELI2	Eurofins Environment Sweden, Lidköping

Uncert. Measurement uncertainty

Symbol description:

* : (Not part of the accreditation)

Performing laboratory if nothing else is stated: Eurofins Food & Agro (Lidköping)

AR-904 v21

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Appendix B. Technical Product/Data Sheets

54

PromOat™

TECHNICAL DATA SHEET: PromOat™ BETA GLUCAN

Description: PromOat™ Beta Glucan is a natural soluble dietary fibre ingredient from oat grain, rich in {1-3, 1-4} beta glucan

Appearance: Fine, cream coloured powder

Origin: 100% Swedish oat grain which is non-GMO
Avena sativa, SW Kerstin variety

1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND COMPANY/UNDERTAKING

Product identity / name	**PromOat™ Beta Glucan**
Product use	Food ingredient / food preparations
Product make-up	Oat kernel extract: Beta glucan soluble fibres and amylodextrins from oat bran
Company	Tate & Lyle Oat Ingredients Älvåsvägen 1 SE 610 20 Kimstad Sweden
Tel no	+ 46 11 25 36 30
Email	oat.info@tateandlyle.com

2. COMPOSITION / INFORMATION ON INGREDIENTS

PromOat™ Beta Glucan is a fraction of milled whole oat grain, derived from the bran, which is gently processed using an alpha-amylase enzyme and physical separation in down-stream processing, and is particularly rich in the soluble fibre component, beta glucan. The product also contains dextrins (amylodextrins) and gluco-oligosaccharides from the oat grain. Insoluble fibre, proteins and oils present in the original oat bran fraction are removed from the product by centrifugation. PromOat™ Beta Glucan is supplied as a drum dried powder.

3. PHYSICAL AND CHEMICAL DATA

PromOat™ Beta Glucan is a fraction of oat bran.

Dietary Fibre Soluble ß glucan	33-36%
Total Dietary Fibre	36-38%
Carbohydrate (dextrin)	54-57%
Protein	<4.5%
Mineral ash	1-3%
Fat	0.5-1%

Supplied with a typical moisture content of 4-6%

Appearance: Fine, cream coloured powder

Density (g/cm^3): circa 0.25

Water solubility: good to moderate

TATE & LYLE

PromOat®
Beta Glucan

PRODUCT DATA SHEET: PromOat® Beta Glucan

Description: PromOat® Beta Glucan is a natural soluble dietary fibre ingredient from oat grain, rich in {1-3, 1-4} beta glucan

Appearance: Fine, cream coloured powder

Origin: 100% Swedish oat grain which is non-GMO
Avena sativa, SW Kerstin variety

Label declaration recommendation: oat beta glucan/ oat bran soluble fibre/ oat fibre/ oat soluble fibre

Supply specification	Value	Typical	Method
Beta glucan (on dry matter)	> 33%	34-36%	AOAC method 995.16
Dry matter	> 93%	94-95%	

Nutritional Data (Values per 100g PromOat®, expressed on dry matter)

Energy	315 kcal or 1319 kJ
Fat	0.5 g
of which saturates	<0.1 g
Carbohydrate (oat maltodextrins)	56 g
of which Sugars	<0.5 g
Fibre (oat beta glucan)	35 g
Protein (N* 6.25)	4 g
Salt	<70mg
Sodium	<25mg

Microbiological data	Value	Method
Total plate count 30° cfu/g	<1000	NMKL Nr 86, 1999
Enterobacteriaceae cfu/g	<10	NMKL Nr 144, 2000
S. aureus cfu/g	<20	NMKL Nr 66, 3 edt. 1999 modified
Yeasts cfu/g	<100	IDF 94B: 1990 modified
Moulds cfu/g	<100	IDF 94B: 1990 modified
Salmonella	negative / 25g	NMKL nr 71, 5 edt. modified
E. coli cfu/g	negative	NMKL nr 125 3 edt. 1996

PromOat® Beta Glucan generates pH 6-7 when dissolved or mixed in water (1%)

Packaging: 15kg plastic lined paper sack.
Bag labelling includes batch code, label declaration and best before date

Pallets: Euro pallets which hold 24 x 15kg bags of PromOat® = 360kg in total

Storage and handling: store in a clean, dry, well-ventilated warehouse at ambient temperature and humidity, away from odorous materials

Best before: 24 months after production date

Tate & Lyle Oat Ingredients, Alvåsvägen 1, 610 20 Kimstad, Sweden t: +46 11 253630 oat.info@tateandlyle.com
Tate & Lyle Oat Ingredients is a trading name of Tate & Lyle Sweden AB
The information given is offered in good faith, but without guarantee. Prospective purchasers are advised to conduct their own regulatory review to determine whether it is possible to make a 'natural' claim in their market.

Appendix C. Stability Test Results

Analysis	Start R	3 mos. R	3 mos. V	3 mos. F	6 mos. R	6 mos. V	6 mos. F	9 mos. R	9 mos. V	9 mos. F
Peroxide number mekv/kg	x	x	x	x	x	x	x	x	x	x
Free fatty acids g/100g	x	x	x	x	x	x	x	x	x	x
Protein content* g/100g	3.9	3.9	3.9	3.8	3.7	3.9	4	3.9	3.9	3.9
Dry matter g/100g	95.5	95.3	96	95.5	95.5	96.3	95.6	94.8	95.8	95.5
Beta-glucan g/100g	34.3	34.6	35.3	34.7	34.3	35	35.7	33.6	34.7	33
Mol. wt. milj.Dalton	2.3	2.2	2.1	2.1	2.2	2.1	2.1	2.1	2.2	1.9
pH 10% solution	5.9	5.9	6	6	5.9	6.1	6.1	5.9	6	6.1
Appearance	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Color	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Smell	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Taste	OK	OK	OK	OK	OK	OK	OK	OK	OK	OK
Vol. wt. kg/l								0.56/0.59	0.56/0.59	0.55/0.58
Total count cfu/g	200	50	50	<50	250	<50	100	<50	<50	<50
Total thermophilic count cfu/g	50	<50	<50	<50	50	150	<50	<50	<50	<50
Enterobact. cfu/g	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
Bacillus.cereus cfu/g	<20	<20	<50	<20	<20	<20	<20	<20	<20	<20
Staph. aureus cfu/g	<20	<20	<50	<20	<20	<20	<20	<20	<20	<20
Yeast cfu/g	<20	<20	<20	<20	<20	<20	<20	<20	<20	<20
Molds cfu/g	<20	20	20	<20	<20	<20	<20	<20	<20	<20
E. coli cfu/g	x	x	x	x	x	x	x	x	x	x

* R - room temperature; V - 40°C; F - freezer (0°C)

000068

Analysis	12 mos. R	12 mos. V	12 mos. F		18 mos. R	18 mos. V	18 mos. F
Peroxide number mekv/kg	x	x	x		x	x	x
Free fatty acids g/100g	x	x	x		x	x	x
Protein content* g/100g	3.9	3.9	3.9				
Dry matter g/100g	94.4	95.3	95.7		94.5	96.2	95.5
Beta-glucan g/100g	35.1	35.2	33.8		33.3	35.3	34.2
Mol. wt. milj.Dalton							
pH 10% solution	5.9	6.1	6.1				
Appearance	OK	OK	OK		OK	OK	OK
Color	OK	OK	OK		OK	OK	OK
Smell	OK	OK	OK		OK	NA	OK
Taste	OK	OK	OK		OK	OK	OK
Vol. wt. kg/l	0.56/0.58	0.56/0.57	0.54/0.59		0.54/0.56	0.55/0.58	0.54/0.56
Total count cfu/g	<50	50	<50		<50	<50	50
Total thermophilic count cfu/g	50	<50	<50		100	<50	<50
Enterobact. cfu/g	<10	<10	<10		<10	<10	<10
Bacillus. cereus cfu/g	<20	<20	<20		<20	<20	<20
Staph. aureus cfu/g	<20	<20	<20		<20	<20	<20
Yeast cfu/g	<20	<20	<20		<20	<20	<20
Molds cfu/g	<20	<20	<20		<20	<20	<20
E. coli cfu/g	x	x	x		x	x	x

- R - room temperature; V - 40°C; F - freezer (0°)

Exhibit I. Report of the Expert Panel

OPINION OF AN EXPERT PANEL ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF OAT β-GLUCAN FOR USE IN FOOD

Introduction

An independent panel of experts, qualified by scientific training and experience to evaluate the safety of food and food ingredients was requested by Tate & Lyle to determine the safety and Generally Recognized As Safe (GRAS) status of oat-derived β-glucan PromOat®. Oat-derived β-glucans are intended for use as a source of dietary fiber for general addition to all foods except infant formula and meat and poultry products. It will be added to foods at per serving levels similar to those of oat β-glucan and barley β-glucan previously notified as GRAS (received "no objection letters") and that will not exceed the amount reasonably required to accomplish its intended technical effect.

A safety review based on the existing scientific literature on the safety of oat β-glucan as well as barley β-glucan (through June 2014) was conducted by ToxStrategies, Inc. and is summarized in their attached dossier. The Expert Panel members reviewed the dossier prepared by ToxStrategies and other pertinent information and agreed to the conclusions described below.

Description

Oat β-glucan consists of polysaccharides of unbranched, linear, mixed-linkage (1-3),(1-4)- β-D-glucans. Oat and barley derived β-glucans contain approximately 70% (1-4) linkages and 30% (1-3) linkages. Typically, blocks of three or four (1-4)-linked β-glucosyl units are connected by (1-3) linkages. Oat-derived β-glucan appears to consist of higher tetrasaccharide and fewer trisaccharide building blocks and may have a higher molecular weight than β-glucan from barley. Furthermore, wheat-derived β-glucan contains an even greater amount of trisaccharides compared to barley-derived β-glucan. In other words, the composition of β-glucans from oat, barley, and wheat form a continuum (FDA 2011, 2013). However, the respective differences are rather small and are unlikely to produce physiological differences (FDA, 2011; FDA, 2013).

The molecular formula for β-D-glucan is $(C_6H_{10}O_5)n$ and the molecular weight of oat β-glucan in commercially available processed food preparations ranges from about 100 kDa to 2000 kDa. The finished product weight-average molecular weight of PromOat® is 2,000 kDa.

Manufacturing Process

Tate & Lyle's PromOat® product is manufactured in a two-step process. It is manufactured following current Good Manufacturing Practice (cGMP) for food (21 CFR Part 110). The first-step is a dry mill process in which the oat grain is dehulled (husk and most of endosperm separated) and milled to specifications. The final output of the dry milling process is oat bran, which is employed in the second processing step, a wet

process. In the wet fractionation process, the oat bran is mixed with water and food use-approved, non-GMO-derived (genetically modified organisms) enzymes at specified temperatures. The mixture is passed through physical separation procedures and sterilized. The process output is insoluble fiber, protein, oat oil, maltodextrin (approved in 21 CFR §184.1444), and oat soluble fiber rich in β-glucan. The maltodextrin and oat soluble fiber (35% β-glucan) components comprise the PromOat® product.

Reagents/processing aids used in the manufacture of oat β-glucan are limited to water and the enzyme alpha-amylase which is commonly used in food ingredient manufacturing processes. No chemical processing aids are employed in Tate & Lyle's manufacturing process. The alpha-amylase enzyme preparation employed in the process is GRAS per 21 CFR §184.1012, complies with Food Chemicals Codex specifications, and is used at levels not to exceed current Good Manufacturing Practice.

Analytical (chemical and microbiological) results for oat β-glucan PromOat® confirm that the finished product meets the proposed specifications, demonstrate the consistency of production, the lack of impurities/contaminants (e.g., heavy metals, pesticides, microbiological toxins), and its stability over an 18-month period.

Functionality

There is common knowledge of a long history of human consumption of oats. Oats have been cultivated around the world for more than 2000 years. The U.S., Germany, Russia, Canada, France, Finland, Poland, and Australia are the largest producers of oats. Numerous food products containing oats are currently marketed in the U.S. and around the world. Oat fiber has become a desirable ingredient for addition to a variety of food products as a source of dietary fiber.

Epidemiological studies and clinical trials have consistently revealed that fiber-rich diets are associated with significant reductions in cardiovascular disease risk. While there is no established dietary reference value (DRV) for soluble fiber, the amount of soluble fiber in a typical mixed diet is one-fourth to one-third of the total dietary fiber intake (ADA, 2008; FDA, 2013).

Dietary Guidelines for Americans (HHS/USDA, 2005) recommend that adults eat half their grains as whole grains, which include oats and wheat. Adequate intake recommendations for adults ≤ 50 years of age are 38g total dietary fiber/day for men and 25g total dietary fiber/day for women (IOM, 2005). For adults greater than 50 years of age, IOM recommends 30 g/day and 21 g/day for men and women, respectively. The guidelines also note that most Americans need to increase their intake of dietary fiber (HHS/USDA, 2005). The daily reference value for dietary fiber is 25 g for a 2000 calorie diet per 21 CFR § 101.9(d).

Intended Use and Intake Assessment

The focus of this GRAS self-determination is for an identical general food use of oat-derived β-glucan (excluding infant formula and meat and poultry) as current barley- and oat-derived β-glucan products as described in GRN 207, 344, and 437. Cargill, in GRAS Notification 344, estimated the combined average intake of barley betafiber by consumers from all uses of barley betafiber (i.e., general food use, and meat and poultry) would be 12.4 g/person/day (8.7 g β-glucan/person/day). The 90th percentile intake was estimated to be 23.5 g/person/day (16.5 g β-glucan/person/day). Cargill stated that barley betafiber would be added to food at levels of 4.3 g/serving, resulting in approximately 3 g of β- glucan/serving. Given the lower level of β-glucan (approximately 35%) in Tate & Lyle's PromOat® product, the estimated intake of β-glucan from the proposed uses of Tate & Lyle's product will be lower by approximately 50% (i.e., 4.35 and 8.25 g β-glucan/person/day for the mean and 90th percentile, respectively). In addition, since use in infant formula, medical foods, and meat and poultry is not being considered as part of this GRAS Notification, the resulting estimated intake will be less than the current GRAS oat- and barley-derived β glucan products that were the subject of GRN Nos. 207, 344, and 437. In summary, the proposed uses of PromOat® will not result in an increase in the overall consumption of β-glucan, but simply provide an alternative source of β-glucan for use in food. Therefore, cumulative intake analysis is not considered necessary.

While Tate & Lyle's PromOat® product could be added at a higher per serving level, the use of oat β-glucan in this manner is considered to be self-limiting for technological reasons such as product texture and/or flavor profile.

Safety Data

Oat β-glucan is found in the cell walls of oat kernels. Beside oats, β-glucan is consumed from other cereals and edible plants such as barley, rye, and wheat. Oat-derived β-glucan concentrates (e.g., Oatrim with a β-glucan content of up to 10% and OatVantage™ with 54% β-glucan) are marketed in the United States and have GRAS status (FDA, 2011; FDA, 2013). Quaker Oats self-determined the GRAS status of Oatrim in 1992 (FDA, 2011). As described in GRAS Notification No. 437 (FDA, 2013), the GRAS status of Oatrim was supported by several factors including 1) Oatrim's similarity to oat starch and maltodextrin (food ingredients with a known safety use profile), 2) the enzymatic manufacturing process was analogous to the biological digestion of starch by humans, and 3) short-term toxicity studies and safety evaluations of Oatrim's constituents did not reveal any areas of concern (FDA, 2011; FDA, 2013). OatVantage™ has similarly been on the market for 10+ years and no safety concerns have been reported.

Numerous studies have been conducted and published in support of the evaluation of the safety of barley β-glucan, including *in vitro* and *in vivo* animal studies as well as clinical studies in humans. While there is a lack of published preclinical safety studies on oat β-glucan, products containing oat β-glucan concentrates have been employed in numerous clinical trials. Other than mild, transient gastrointestinal (GI) effects such as flatulence and abdominal discomfort, no significant adverse effects were noted. It should be noted

that these GI effects commonly occur following a shift from a low- to high-fiber diet (IOM, 2005). Updated literature searches covering the period of 2010 – present have revealed no recent studies that report safety concerns.

Epidemiological studies and clinical trials have consistently revealed that fiber-rich diets are associated with significant reductions in cardiovascular disease risk and other health benefits. The intended uses of PromOat® have the potential to increase the dietary fiber intakes among the US population. The Institute of Medicine (2005) reviewed the possible effect of cereal fiber on mineral absorption (e.g., iron, zinc, calcium, magnesium) and determined that dietary fiber, as part of a balanced diet, has not been found to adversely affect mineral status in healthy people at recommended intake levels.

Children with atopic dermatitis and farmers with allergies to grain dust may experience allergic reactions to oat proteins. These proteins can act as skin and respiratory allergens (Boussault et al., 2007; FDA, 2013).

Allergy manifestation resulting from consumption of oats and oat products has been the subject of debate. It has been alleged that oats may cause adverse effects in individuals with celiac disease. As a result, use of oats in gluten-free diet was not allowed. Evidence from more recent reports indicates that oats are safe for consumption by most individuals with celiac disease (Rashid et al., 2007).

For instance, Health Canada (2007) critically reviewed the scientific literature and concluded that the majority of people with celiac disease can tolerate moderate amounts of pure oats that are uncontaminated with other cereal grains such as wheat, barley and rye. The Canadian Celiac Association stated that in past years, oats were not allowed in a gluten-free diet and were considered to be averse to persons with celiac disease. However, based on recent data, pure oats, uncontaminated with other gluten-containing grains, if consumed in limited amounts, are safe for most of those with celiac disease. Health Canada supported this position, indicating that persons with celiac disease can tolerate some amounts of pure oats (uncontaminated with other cereal grains such as wheat, barley and rye). In fact, pure oats may be beneficial to persons with celiac disease, as its palatability may increase patients' compliance with a gluten-free diet (Health Canada, 2007).

Oat consumption by celiac disease patients is not widely recommended in the U.S. due to concerns of potential contamination of commercial oats (Kupper, 2005; American Celiac Society, 2014). According to the National Foundation for Celiac Awareness (NFCA, 2014), although oats do not contain gluten, a small percentage of persons with celiac disease react to pure, uncontaminated oats. Further, most mills that process oats also manufacture grains which contain gluten, making cross contamination likely. However, up to 50 g/day of dry, gluten-free oats is considered safe (NFCA, 2014).

The potential allergenicity of β-glucan was evaluated in the available literature, but no relevant information was located. Natural sources of β-glucan concentrates, such as barley, have been safely consumed for decades. β-glucan is not listed among FDA's list

of the 8 major food allergens (FDA, 2010). The lack of available information and absence from FDA's allergen list leads to the conclusion that allergic reactions to β-glucan itself are not of concern.

In summary, the evaluations of the possible effects of oats, cereal fiber and/or β-glucan on mineral absorption and allergenicity have been considered by the U.S. FDA and EFSA and found not to present a safety concern as consumed as part of the normal diet.

Conclusions of the Expert Panel

We, the undersigned members of the Expert Panel, have individually and collectively critically reviewed the published and ancillary information pertinent to the identification, use and safety of the oat-derived β-glucan PromOat®. We conclude that oat-derived β-glucan produced by Tate & Lyle under the conditions described in the attached dossier and meeting Tate & Lyle specifications is safe.

We also conclude that the intended use of oat-derived β-glucan in food, meeting the specifications described above, is Generally Recognized As Safe (GRAS) based on scientific procedures.

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9/8/14

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Submission End