ORIGINAL SUBMISSION

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

D-Ribose as defined in the report in Appendix I entitled, " **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE"**, dated November 29, 2007, has been determined to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act.* This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of D-ribose in food as described below is exempt from the requirement of premarket approval.

Signed,

1-16-08

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

Date

01-22-08 F05:53 RCVD

B. Name and Address of Notifier

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

C. Common Name of the Notified Substance

D-ribose

D. Conditions of Intended Use in Food

Bioenergy, Inc. intends to market D-ribose as an ingredient in beverages and beverage bases (calorie-reduced non-cola carbonated beverages, non-cola carbonated beverages, non milk-based meal replacements, sports, isotonic, and energy drinks), coffee and tea (instant tea, specialty and spiced teas), frozen dairy desserts and mixes (frozen yogurt, ice cream and frozen milk desserts (excluding novelties)), grain products and pasta (energy and meal replacement

bars), hard candy (selected hard candy), milk products (milk-based meal replacements, milk drinks (no malts or shakes), yogurts), processed fruits and fruit juices (calorie-reduced fruit drinks and ades, fruit juices, fruit nectars), processed vegetables and vegetable juices (vegetable juice) and soft candy (selected soft candy (excluding chocolate bars)) [see Appendix I - **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

The consumption of D-ribose from all proposed food uses was estimated using the proposed food uses and use levels in conjunction with food consumption data included in the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2007).

Approximately 83.4% of the total U.S. population was identified as consumers of D-ribose from the proposed food-uses (6,893 actual users identified). On an all-user basis, the mean intake of D-ribose by the total U.S. population from all proposed food-uses was estimated to be 3.39 g/person/day or 68.01 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of D-ribose the total U.S. population from all proposed food-uses was estimated to be 7.24 g/person/day or 153.45 mg/kg body weight/day.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, D-ribose has been determined to be GRAS on the basis of scientific procedures (U.S. FDA, 2007a). This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of D-ribose as a component of food. The safety of the ingredient is based on the results of published toxicological and clinical studies in animals and humans on D-ribose. The GRAS status of D-ribose is based on this available published scientific information in relation to the intended conditions of use of the ingredient in foods. [See Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

Should the FDA have any questions or additional information requests regarding this notification, Bioenergy, Inc. will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

D-Ribose is a white to slightly yellow crystalline powder, characterized by a fruity sweet odor and slightly sweet taste. It is chemically related to other 5-carbon monosaccharides, such as arabinose and xylose.

Common or Usual Name: D-ribose

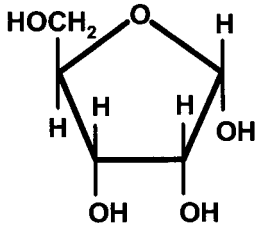
Chemical Name: A-D(-) ribofuranose

Chemical Abstracts Service (CAS) Number: 50-69-1

Empirical Formula: $C_5H_{10}O_5$

Molecular weight: 150.13

Structural Formula:



B. Method of Manufacture

D-ribose is produced by a non-genetically modified and non-sporulating strain of the microorganism *Bacillus subtilis* (*B. subtilis*), which accumulates D-ribose due to low transketolase activity, resulting in the inability of the organism to utilize this sugar. Transketolase is an enzyme that catalyzes the transfer of a 2-carbon fragment from xylulose 5-phosphate to ribose 5-phosphate, producing glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate. The disruption in the metabolic pathway for D-ribose results in its accumulation.

In the U.S., carbohydrase (21 CFR §184.1148 [U.S. FDA, 2007b]) and protease (21 CFR §184.1150 [U.S. FDA, 2007c]) from *B. subtilis*, meeting food-grade specifications, are affirmed as GRAS for use in foods as enzymes at levels not exceeding current good manufacturing practice (cGMP) (U.S. FDA, 2007b,c). The affirmations are predicated on the use of nonpathogenic and nontoxigenic strains of *B. subtilis* (U.S. FDA, 2007b,c).

B. subtilis has traditionally been used in the commercial production of the Japanese delicacy natto by fermentation of soybeans, as well as in the commercial production of other compounds utilized in the food industry. Furthermore, *B. subtilis* is widely distributed in the environment and is naturally present in many foods that have been consumed by humans for decades with no evidence of food poisoning (Hui *et al.*, 2004; Logan *et al.*, 2007).

Following a careful review of the scientific and medical literature, Professor Eric Johnson (Food Research Institute, University of Wisconsin-Madison) concluded that *B. subtilis* is non-toxigenic and non-pathogenic. He also noted that antibiotic resistance would not be expected as there are no known plasmids in *B. subtilis* that encode for antibiotic resistance, and because D-ribose-producing strains of *B. subtilis* were developed through a process that does not lead to antibiotic resistance (UV mutagenesis).

The production of D-ribose is initiated by cultivating *B. subtilis* in a nutrient-rich medium, followed by fermentation. During fermentation, glucose is converted to D-ribose, which accumulates in the culture broth. The culture broth is filtered to remove bacterial cells and undergoes extensive purification, followed by concentration through evaporation and crystallization with ethanol. The crystals are recovered by centrifugation, then dried and packaged. The final product is of high purity (97 to 103% ribose).

C. Specifications for Food Grade Material

In order to ensure a consistent product, Bioenergy, Inc. established numerous specification parameters of the final ingredient (see Table 1), and representative lots of the manufactured product are routinely analyzed to verify that the manufacturing process produces a consistent product within final product physical, chemical, and microbiological parameters. D-ribose is produced in accordance with current Good Manufacturing Practices and meets appropriate food-grade specifications, and all raw materials and processing aids used in the manufacture of D-ribose, including water, activated carbon, sodium chloride, hydrochloric acid, ethanol, ion exchange resin, and defoaming agent, are permitted for use in food in the U.S. Furthermore, comprehensive analyses of potential residues from the manufacturing process have confirmed the purity of the final product (97 to 103% pure). For example, analytical procedures failed to detect the presence of yeasts, moulds, *Salmonella,* or *Escherichia coli.* Moreover, no proteins were detected in samples of 20% D-ribose solution as measured by the Bradford assay. Ethanol, as along with sugars and sugar alcohols produced in the fermentation process also are largely removed during purification.

Table 1 Chemical and Physical Specifications for D-Ribose

Specification Parameter	Specification	Method of Analysis
Appearance	Dry shape-holding characteristics with powdery texture that is white to slightly yellow in color.	Internal method (SOP-QC002-00)
Melting point	80 to 90°C	Internal method (derived from method I, CP2005 Appendix VI C)
Specific rotation	-19.0 to -21.0°	CP2005 Appendix VI E
D-ribose (purity)	97.0-103.0%	Internal method (SOP-QC002-00)
Loss on drying (moisture)	<2.0%	Internal method (derived from method I, CP2005 Appendix VIII L)
Ash	≤0.2%	CP2005 Appendix VIII N
Clarity of solution	≥95% transmittance	Bioenergy 30-014
Lead	≤0.1 ppm	AOAC 993.14
Arsenic	≤1 ppm	Method I, CP2005 Appendix VIII J
Total plate count	NMT 100 CFU/g	AOAC 990.12
Salmonella sp.	Negative/25g	AOAC 991.14
Coliforms	NMT 10 CFU/g	AOAC 992.21
Yeast and mold	NMT100 CFU/g	AOAC 992.11

Abbreviations: CFU, colony forming unit; NMT, not more than

III. Self-Limiting Levels of Use

There are no self-limiting technical attributes of D-ribose that would limit its use.

IV. Basis for GRAS Determination

The determination that D-ribose is GRAS is on the basis of scientific procedures. [See Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

V. References

CDC. 2006. Analytical and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES). Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS); Hyattsville, Maryland. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf.

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U.S. FDA. 2007. Part 184—Direct food substances affirmed as generally recognized as safe. Section §184.1148—Bacterially-derived carbohydrase enzyme preparation. In: U.S. Code of Federal Regulations (CFR). Title 21: Food and Drugs (U.S. Food and Drug Administration). U.S. Food and Drug Administration (U.S. FDA). U.S. Government Printing Office (GPO); Washington, DC, pp. 500-501. Available from: http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr184.1148.pdf.

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USDA. 2007. What We Eat in America: National Health and Nutrition Examination Survey (NHANES): 2003-2004. U.S. Department of Agriculture (USDA); Riverdale, Maryland. Available from: http://www.ars.usda.gov/Services/docs.htm?docid=13793#release.

Appendix 1

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE

November 29, 2007

At the request of Bioenergy, Inc. (Bioenergy), an Expert Panel of independent scientists consisting of Dr. James Anderson (University of Kentucky), Dr. Joseph Borzelleca (Virginia Commonwealth University, Medical College of Virginia), and Dr. Robert Nicolosi (University of Massachusetts Lowell) was convened on August 17, 2007 to determine the safety and the GRAS status of D-ribose for use as an ingredient in beverages and beverage bases (calorie-reduced non-cola carbonated beverages, non-cola carbonated beverages, non milk-based meal replacements, sports, isotonic, and energy drinks), coffee and tea (instant tea, specialty and spiced teas), frozen dairy desserts and mixes (frozen yogurt, ice cream and frozen milk desserts (excluding novelties)), grain products and pasta (energy and meal replacement bars), hard candy (selected hard candy), milk products (milk-based meal replacements, milk drinks (no malts or shakes), yogurts), processed fruits and fruit juices (calorie-reduced fruit drinks and ades, fruit juices, fruit nectars), processed vegetables and vegetable juices (vegetable juice) and soft candy (selected soft candy (excluding chocolate bars)). The *curriculum vita of each Panelist is* attached (Attachment I). The *curricula vitae* detail the scientific training and experience of each Panelist and provide evidence of each Panelist's qualifications for evaluating the safety of food ingredients.

The Panel, independently and collectively, critically evaluated a comprehensive package of scientific information and data compiled from searches of the published literature and other sources by Cantox Health Sciences International through July 2007. Medline, Toxline, and EMBASE served as the primary source of published literature on the safety of D-ribose. Additionally, the Panel evaluated other information deemed appropriate or necessary including data and information provided by Bioenergy. This included information pertaining to the method of production and product specifications, analytical data, and intended uses.

Following critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, D-ribose, meeting appropriate food-grade specifications, is GRAS based on scientific procedures. The safety of the ingredient is based on the results of published toxicological and clinical studies in animals and humans on D-ribose. The GRAS status of D-ribose is based on this available published scientific information in relation to the intended conditions of use of the ingredient in foods. A summary of the basis for the Panel's conclusion, excluding confidential information, is provided below.

Manufacturing, Composition, and Stability

D-ribose is produced by a non-genetically modified and non-sporulating strain of the microorganism *Bacillus subtilis* (*B. subtilis*), which accumulates D-ribose due to low transketolase activity, resulting in the inability of the organism to utilize this sugar. Transketolase is an enzyme that catalyzes the transfer of a 2-carbon fragment from xylulose 5-phosphate to ribose 5-phosphate, producing glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate. The disruption in the metabolic pathway for D-ribose results in its accumulation.

In the U.S., carbohydrase (21 CFR §184.1148 [U.S. FDA, 2006a]) and protease (21 CFR §184.1150 [U.S. FDA, 2006b]) from *B. subtilis*, meeting food-grade specifications, are affirmed as Generally Recognized as Safe (GRAS) for use in foods as enzymes at levels not exceeding current good manufacturing practice (cGMP) (U.S. FDA, 2006a,b). The affirmations are predicated on the use of nonpathogenic and nontoxigenic strains of *B. subtilis* (U.S. FDA, 2006a,b).

B. subtilis has traditionally been used in the commercial production of the Japanese delicacy natto by fermentation of soybeans, as well as in the commercial production of other compounds utilized in the food industry. Furthermore, *B. subtilis* is widely distributed in the environment and is naturally present in many foods that have been consumed by humans for decades with no evidence of food poisoning (Hui *et al.*, 2004; Logan *et al.*, 2007).

Following a careful review of the scientific and medical literature, Professor Eric Johnson (Food Research Institute, University of Wisconsin-Madison) concluded that *B. subtilis* is non-toxigenic and non-pathogenic. He also noted that antibiotic resistance would not be expected as there are no known plasmids in *B. subtilis* that encode for antibiotic resistance, and because D-ribose-producing strains of *B. subtilis* were developed through a process that does not lead to antibiotic resistance (UV mutagenesis).

The production of D-ribose is initiated by cultivating *B. subtilis* in a nutrient-rich medium, followed by fermentation. During fermentation, glucose is converted to D-ribose, which accumulates in the culture broth (conversion rate of 33 to 35%). The culture broth is filtered to remove bacterial cells and undergoes extensive purification, followed by concentration through evaporation and crystallization with ethanol. The crystals are recovered by centrifugation, then dried and packaged.

Chemical and microbiological specifications of D-ribose meet appropriate specifications for food grade material in terms of purity and content for the intended conditions of use. Specifications are attached as Table 1. Chemical analysis of 5 manufactured lots confirms that the manufacturing process results in a consistent product and meets the proposed specifications.

It is unlikely that the microorganism (*B. subtilis*) would be present in the final product given the purification process. This is supported through the high level of purity of the final product (97 to

103% ribose) and the fact that analytical procedures failed to detect the presence of yeasts, moulds, *Salmonella,* or *Escherichia coli*. Furthermore, no proteins were detected in samples of 20% D-ribose solution as measured by the Bradford assay.

Ethanol, along with sugars and sugar alcohols produced in the fermentation process are largely removed during purification.

The stability of Bioenergy D-ribose products has been studied in poly bags stored at room temperature (the standard package and storage condition for Bioenergy D-ribose). All the microbe counts remained consistent and well within the limit of specifications during the 24-month test. The product settled and became slightly yellow during storage. However, the individually tied double poly bags kept the moisture content low. The bulk density and purity of the product decreased slightly but remained within specification during the 24-month period.

Background Dietary Intake, Proposed Uses and Estimated Intake

D-Ribose occurs naturally in the human diet as it is present in all living cells as a component of genetic material and several chemicals involved in metabolism. It is estimated that daily endogenous production of D-ribose ranges from approximately 3 to 19 g/day[1].

D-Ribose is proposed for use as an ingredient in beverages and beverage bases (calorie-reduced non-cola carbonated beverages, non-cola carbonated beverages, non milk-based meal replacements, sports, isotonic, and energy drinks), coffee and tea (instant tea, specialty and spiced teas), frozen dairy desserts and mixes (frozen yogurt, ice cream and frozen milk desserts (excluding novelties)), grain products and pasta (energy and meal replacement bars), hard candy (selected hard candy), milk products (milk-based meal replacements, milk drinks (no malts or shakes), yogurts), processed fruits and fruit juices (calorie-reduced fruit drinks and ades, fruit juices, fruit nectars), processed vegetables and vegetable juices (vegetable juice) and soft candy (selected soft candy (excluding chocolate bars)). The proposed food uses and use-levels are provided in Table 2.

Estimates for the intake of D-ribose were based on the proposed food-uses and use-levels in conjunction with food consumption data included in the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2006). Consumption data and information pertaining to the individual proposed food-uses of D-ribose were used to estimate the all-person and all-user intakes of D-ribose for specific demographic groups and for the total U.S. population.

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[1] The estimated mean daily intake of carbohydrates in the U.S. is 321 and 242 g in men and women, respectively (CDC, 2004). Depending on the tissue or cell type, 2 to 9% of glucose is utilized *via* the pentose phosphate pathway (Magnusson *et al.*, 1988; Delgado *et al.*, 2004). Assuming that 2/3 of dietary carbohydrates are composed of glucose (assuming that sucrose (metabolized to glucose and fructose), lactose (metabolized to glucose and galactose), and maltose (metabolized to 2 molecules of glucose) are consumed equally), the amount of D-ribose formed endogenously through the pentose phosphate pathway ranges from 3.2 (242 g/day in women x 2/3 x 2%) to 19.3 g/day (321 g/day in men x 2/3 x 9%).

In summary, 83.4% of the total U.S. population was identified as consumers of D-ribose from the proposed food-uses (6,893 actual users identified). On an all-user basis, the mean intake of D-ribose by the total U.S. population from all proposed food-uses was estimated to be 3.39 g/person/day or 68.01 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of D-ribose the total U.S. population from all proposed food-uses was estimated to be 7.24 g/person/day or 153.45 mg/kg body weight/day.

Regulatory Status

A pre-market notification for new dietary ingredients (NDI) for D-ribose (manufactured by Bioenergy) was submitted by Humanetics Corp. in 1997 (U.S. FDA, 1997). The U.S. Food and Drug Administration (FDA) raised no questions regarding the use of D-ribose as a dietary supplement at doses up to 20 g per day in liquid or capsule form.

Similarly, FDA raised no questions in response to a pre-market notification submitted by Leiner Health Products for the use of D-ribose (manufactured by Bioenergy) as a dietary supplement providing up to 12 g per day in powder form, and 3 g per day in tablet form (U.S. FDA, 2000).

Data Pertaining to Safety

The evaluation of the safety of D-ribose was primarily based on its natural occurrence and role in the functioning of all living cells, as well as on data from metabolic studies in animals and humans, a subchronic oral toxicity study and an embryotoxicity/teratology study conducted on Bioenergy's D-ribose in rats, *in vitro* and *in vivo* genotoxicity assays utilizing Bioenergy's D-ribose or ribose from other manufacturers, and human studies conducted on D-ribose manufactured by Bioenergy or by other companies.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Systemic Exposure from Endogenous Ribose Production

D-Ribose is synthesized naturally in all living cells *via* the pentose phosphate pathway. The pentose phosphate pathway serves two major functions in metabolism: 1) generation of NADPH as a source of reducing equivalents for biosynthetic reactions and 2) formation of ribose-5-phosphate as the initial step in purine and pyrimidine synthesis.

Exposure from Exogenous Sources of D-Ribose

Orally administered D-ribose has been shown to be 87.8 to 99.8% absorbed in humans (Gross *et al.*, 1989). Once absorbed, D-ribose is phosphorylated and enters the pentose phosphate pathway of glucose metabolism as a substrate for purine and pyrimidine biosynthesis. Excess D-ribose is converted to hexoses (including glucose) or triose intermediates of glycolysis. Confirmation of the conversion process resulted following oral, i.v., or i.p. administration of ^{14}C-ribose or ^{3}H-ribose to animals or humans, or incubation of radiolabeled ribose with tissues

or cells, when radiolabel was detected in glucose (Horecker *et al.*, 1954; Katz *et al.*, 1955; Hiatt, 1958; Segal and Foley, 1958), glycogen (Bloom *et al.*, 1956; Hiatt, 1957; Gonçalves *et al.*, 1969), glycoproteins (Gonçalves *et al.*, 1969), nucleic acids (Hiatt, 1957; Coffey *et al.*, 1966; Gonçalves *et al.*, 1969), and in expired carbon dioxide (Katz *et al.*, 1955; Agranoff and Brady, 1956; Bloom *et al.*, 1956; Segal and Foley, 1958). No recently published studies pertaining to D-ribose metabolism were identified in the literature.

Ingested D-ribose is phosphorylated *via* membrane bound ribokinase as it crosses the cell wall before entering the pentose phosphate pathway downstream of the gatekeeper enzymes glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, making it available for flux down the purine nucleotide pathway of purine and pyrimidine synthesis. When pentose phosphates are not needed for purine nucleotide synthesis in muscle, or when ribose is present in excess amounts, pentose phosphates are recycled through glycolysis mainly in the liver *via* conversion into fructose-6-phosphate, fructose-1,6-bisphosphate (to a lesser degree), and glyceraldehyde-3-phosphate, eventually to form CO_2 and water and yielding energy *via* adenosine triphosphate (ATP) turnover. Fructose-6-phosphate is further converted to glucose-6-phosphate, which in turn is converted to glucose-1-phosphate and incorporated into glycogen for storage. Glycogen, glucose, and glycolytic intermediates, as formed from D-ribose *via* the pentose phosphate pathway, are naturally occurring carbohydrates that are metabolic products of dietary carbohydrates.

In summary, evidence indicates that D-ribose is well absorbed in humans. Once absorbed, D-ribose is phosphorylated and enters the pentose phosphate pathway of glucose metabolism as a substrate for purine and pyrimidine biosynthesis. Excess D-ribose is converted to hexoses (including glucose, a constituent of many dietary carbohydrates) or triose intermediates of glycolysis.

Toxicological Studies

Subchronic and Chronic Studies

In a study reported by Griffiths *et al.* (2006a) and conducted in accordance with Good Laboratory Practices (GLP) (OECD, 1988), FDA Redbook guidelines (U.S. FDA, 1982), and Organisation for Economic Cooperation and Development (OECD) Guideline 408 (OECD, 1998), groups of 5-week-old albino Wistar rats (20 male and 20 female per group) were administered diets (modified pelleted commercial rodent diet [Rat & Mouse No. 3 Breeding Diet (RM3)] in which 20% of the barley was replaced by the test article and/or pregelatinized potato starch) containing 0, 5, 10, or 20% D-ribose provided by Bioenergy (equivalent to mean daily intakes of 0.0, 3.6, 7.6, and 15.0 g/kg body weight/day in males and 0.0, 4.4, 8.5, and 15.7 g/kg body weight/day in females) for 13 weeks.

No treatment-related deaths occurred during the study. The authors reported mean body weight in all treated animals was decreased relative to the controls, with statistical significance

in high-dose animals from Day 7 onwards and in mid-dose females throughout most of the study. In mid-dose males and low-dose males and females, significant decreases in weight were observed sporadically and less frequently. Mean body weight of high-dose males was 87% of the control on Day 91, but all other treatment groups were within 10% of the control. The authors reported mean feed consumption and mean feed conversion efficiency to be similar across all groups. A dose-related increase in water consumption occurred across all groups as the study progressed. The mean water intake of the treatment groups did not differ significantly from the controls but the many individual daily values within the weekly measurements were significantly higher for the mid- and high-dose groups compared to controls. No significant differences were observed in the ophthalmoscopic examination.

Statistically significant effects in hematological measurements were considered unrelated to treatment because they were sporadic and non-dose-responsive, or because values were within historical control ranges. Most of the significant changes in clinical chemistry measurements were only observed in the high-dose treatment groups. The authors stated that the decreased total protein in treated males resulted from a control value that was abnormally high relative to historical controls. Cholesterol, triglyceride and phospholipid concentrations were decreased in the high-dose males and non-significantly decreased in females. The urinary concentrations of several parameters were decreased in D-ribose-treated animals, but the authors considered these decreases to be the result of dilution caused by increased urinary volume. Urine pH in fasted animals was significantly decreased in high-dose females compared to controls, but no differences were observed in males.

Significant changes in terminal body weights and a number of changes in absolute and relative organ weights were reported. Terminal body weights in high-dose males and mid- and high-dose females were significantly decreased. Relative kidney weight was increased in all treated males and relative liver weight was increased in mid-dose males and all treated females. The effects on absolute liver weight were inconsistent. Absolute and relative cecal weights were reported to be significantly increased in a dose-dependent manner in both sexes. Absolute brain weights were decreased in high-dose animals, but relative weights were increased in mid-dose females and high-dose males and females. Relative spleen weight was increased in mid- and high-dose animals, and absolute lung weights were decreased in high-dose animals. The authors concluded that most of these effects occurred as a physiological adaptive response to the high levels of carbohydrates in the diet, and that enlargement of the cecum and liver has commonly been reported after high-level carbohydrate exposure. Furthermore, the organ weight changes were not accompanied by histopathological effects.

At necropsy, no consistent macroscopic pathological findings were noted other than the yellow discoloration of abdominal fur in all mid-and high dose animals from Weeks 8 and 12, respectively, onward. This was considered to be the result of excess urinary output. Microscopic evaluation of numerous tissues revealed no changes that could be attributed to treatment, as all findings were typical of this strain and age of rats and appeared to be randomly

distributed among treated and control groups. No treatment-related changes in hepatocellular morphology were observed upon staining of liver sections with hematoxylin and eosin (H&E) and periodic acid-Schiff (PAS). Screening for neurotoxicity revealed no effects of D-ribose treatment.

The authors stated that 20% D-ribose in the diet could be considered as a potential no-observed-adverse-effect level (NOAEL) due to their opinion that the effects observed at this dose level were not toxicologically significant and likely represented a physiological effect. It was concluded that an undisputable no-observed-effects level (NOEL) for D-ribose could be established at the 5% level in the diet, which is equivalent to an average daily intake of 3.6 and 4.4 g/kg body weight/day for males and female rats, respectively. However, increased cecal weight was the only organ weight effect noted in the study that occurred in a dose-dependent manner. Cecal weight increases are common findings in rodents fed excess amounts of materials, such as carbohydrates. As a result, the increased cecal weight reported in this study is considered a physicological rather than toxicological response. Based upon the adaptive responses known to occur as a result of high carbohydrate intake, a NOAEL of 20% D-ribose in the diet, equivalent to an average daily intake of 15.0 and 15.7 g/kg body weight/day for male and female rats, respectively, was concluded.

Reproductive and Developmental Studies

In an embryotoxicity/teratogenicity study conducted in accordance with GLP (OECD, 1988), FDA Redbook guidelines (U.S. FDA, 1982), and OECD Guideline 414 (OECD, 2001), 12-week-old albino Wistar rats were mated and the females were administered D-ribose (provided by Bioenergy) in the diet (modified pelleted commercial rodent diet [Rat & Mouse No. 3 Breeding Diet (RM3)] in which 20% of the barley was replaced by the test article and/or pregelatinized potato starch) from Gestational Day (GD) 0 of gestation until Caesarean section on GD 21 (Griffiths *et al.*, 2006b). The rats were exposed (28 animals per dose) to D-ribose at 0, 5, 10, or 20% of the diet, which equates to approximately 0.0, 4.25, 7.94, and 9.91 g/kg body weight/day, respectively.

All animals survived to Day 21 and clinical observations of the animals' appearance, general condition and behavior were reported to be unremarkable. Mean body weight gain and food consumption were significantly reduced in the mid- and high-dose groups over the first two weeks of the study. However, during the last week of the study the mid- and high-dose groups had a significantly greater rate of weight gain, resulting in no significant difference between the groups by the end of the study. At necropsy, gross observations were reported to be unremarkable. The absolute and relative weights of the liver were not significantly different at any dose level compared to controls. Both absolute and relative cecal weights were reported to be significantly increased at all dose levels *versus* controls. There was no difference in the gravid uterus weights or the carcass weights of the treated groups and the control.

The authors reported no significant difference in the reproductive parameters between the control and treated groups. External observations of fetuses and placentas did not differ among study groups. The fetotoxicity data revealed no significant differences between treated and control groups in mean fetal and placental weights. Visceral abnormalities were unremarkable and did not differ between the control and treated groups. Significant skeletal malformations were not observed in any of the study groups. There were no significant differences in the incidences of one or multiple wavy ribs in the control or test animals, but testing of the combined fetal and litter incidences revealed a significantly higher incidence in the mid- and high-dose groups compared to control animals. The authors considered a number of variations in skeletal ossification to be sporadic and non-dose responsive; however, they did report significant differences between control and treated groups in the incidences of incomplete ossification of the frontal, parietal and interparietal bones. The fetal incidence of incomplete ossification of the frontal bone was lower in D-ribose-treated fetuses than in control animals, and the fetal incidence of incomplete ossification of the parietal bone was not dose-dependent (lower incidence in the 20% D-ribose group compared to the 10% D-ribose group).

The authors considered the effects on cecal weight as a nutritional effect due to the high carbohydrate levels in the D-ribose-containing diets, and that cecum enlargement is commonly reported in rats after exposure to high levels of carbohydrates. They also stated that the noted skeletal anomalies and variations in ossification of cranial bones have been previously reported in Wistar rats (as well as other rat strains), and that these effects are generally described as reversible (Kavlock *et al.*, 1982; Manson and Kang, 1994; Kruger *et al.*, 1999). These effects are likely due to the disruption of maternal nutrition and homeostasis by the large amounts of monosaccharides ingested in the test diets, as evidenced by the effects on maternal food consumption and body weight change, and particularly by the markedly increased maternal relative cecal weight in the D-ribose groups compared to control animals.

Because there were no significant differences in the incidence of malformations between treatment and control groups, it was concluded by the authors that a NOAEL for teratogenicity could be established at 20% D-ribose in the diet (9.91 g/kg body weight/day), and that a "clearly undisputable NOAEL for developmental toxicity" was 5% of the diet, corresponding to an average daily D-ribose intake of between 3.64 and 4.61 g/kg body weight/day. It should be noted that this dose, which was the lowest dose tested in the study, was approximately 4 times higher than the limit dose (1 g/kg body weight/day) for reproductive toxicity studies recommended by the International Conference on Harmonisation (ICH, 1993).

Mutagenicity/Genotoxicity Studies

Four unpublished studies investigating the potential genotoxicity of Bioenergy's D-ribose have been conducted. These include a bacterial reverse mutation test conducted in *Salmonella typhimurium* and *E. coli*, a chromosomal aberration assay in Chinese hamster ovary cells, a mammalian gene mutation test conducted in cultured mouse lymphoma L5178Y cells, and an *in*

vivo bone marrow micronucleus study in mice (van Ommen, 1999; de Vogel, 2000a,b; Steenwinkel, 2000). The potential mutagenicity of D-ribose from other sources has also been evaluated in 2 published reports of bacterial reverse mutation tests conducted in *S. typhimurium* (Aiyar and Subba Rao, 1977; Wilmer *et al.,* 1981).

Results from *in vitro* and *in vivo* studies indicate that D-ribose is not genotoxic in bacterial or mammalian cells. Furthermore, given that D-ribose is a simple 5-carbon sugar that is used to synthesize genetic material, genotoxic activity would not be expected.

Clinical Studies

In a study reported by Seifert *et al.* (2001), (Seifert *et al.,* 2001 [abstract]), 21 healthy, non-diabetic adults (12 male and 7 females completed the study) were administered 10 grams D-ribose (provided by Bioenergy) twice daily for 14 days. Daily diet and exercise habits were maintained during the study. Blood was collected at baseline and on days 7 and 14 and complete blood count (CBC), albumin, alkaline phosphatase (ALK P), gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid and glucose levels were measured. The authors reported no clinically adverse symptoms or events, including gastrointestinal problems, in any subject during the study. No significant differences from baseline to the end of the study were observed for hemoglobin, hematocrit, red blood cell count, white blood cell (WBC) count, platelet count, ALK P, GGT, ALT, AST, glucose and uric acid. However, the authors reported an increase in AST (from 16.9 to 21.8 U/L) and uric acid (from 5.24 to 5.88 mM/L) from baseline at Day 7, followed by a decrease at Day 14. Blood glucose levels declined, but not significantly, over the trial. The levels were reported to be 3.64, 3.55, and 3.23 mM/L on Days 0, 7, and 14, respectively. The decrease was less pronounced in males compared to females (3.44 to 3.20 *vs.* 3.85 to 3.31 mM/L from baseline to Day 14). The authors reported no significant differences between the genders in terms of hemoglobin, hematocrit, ALT, albumin, and platelet counts. However, a decrease in WBC levels in females and an increase in males over the 14-day period were reported (6.22 to 5.69 x 10^3/μL and 6.13 to 6.25 x 10^3/μL, respectively). No significant changes in ALK P levels were observed in males, but an increase was reported in females on Day 14 (63.6 to 67.7 U/L). GGT levels in males were reported to be decreased on Day 7 but a trend toward baseline levels was noted on Day 14 (27.6, 22.7, and 25.4 U/L, respectively). No change was observed in females. In all subjects, GGT levels decreased at Day 7 but returned to baseline at Day 14 (21.2, 18.3, and 20.3 U/L, respectively). AST levels increased in all subjects (16.9 to 20.6 U/L). Males were reported to have a significantly increased AST level on Day 14 (21.3 to 25.6 U/L) and females on Day 7, with less of an elevation at Day 14 (12.4, 19.6 and 15.7 U/L, respectively). All enzyme values were within the reported normal ranges for each parameter (Murray *et al.*, 2000). The authors concluded that ingestion of 20 grams of D-ribose per day for 14 days did not produce significant adverse changes in hematological or biochemical parameters. They suggested that the increase in uric acid levels may have resulted from an increase in the synthesis of purine nucleotides.

Fenstad *et al.* (2000) (Frelich and Seifert, 2001 [abstract]) also investigated the effects of Bioenergy's D-ribose on carbohydrate and purine metabolism. Ten healthy, non-diabetic male and female subjects (6 between the ages of 24 and 30 and 4 between the ages of 40 and 50) were given oral doses of 0, 2, 5, and 10 g of D-ribose dissolved in 250 mL of water after an overnight fast. Each subject was instructed to maintain a consistent diet and to abstain from alcohol, caffeine and exercise 24 hours before the start of the trial and throughout the trial. Four to 11 days elapsed between each tested dose. Blood samples for glucose, insulin, uric acid and lactate were obtained at 0, 15, 30, 45, 60, and 120 minutes after the consumption of each dose. Oxygen uptake was measured at 0, 15, 45, and 75 minutes after ingestion. The authors reported that no adverse effects occurred at any dose. Baseline blood glucose levels were reported to be normal for all subjects. Blood glucose levels at doses of 2 and 5 g D-ribose were not significantly different from baseline. In fact, glucose levels were higher than control values following administration of 2 g D-ribose, although the difference was not significant. After consumption of 10 g D-ribose, a significant decrease in blood glucose (33%) was observed at the 45 and 60 minute time points, with a return to baseline approximately 2 hours post-ingestion. These effects were reported to be the same in both age groups. D-Ribose-induced hypoglycemia was temporary and was not associated with any adverse symptomatic events. Insulin levels peaked at 15 minutes after administration, then decreased to or below baseline, but neither change was significant. No significant differences in insulin levels were reported between treated and control groups. Although a non-significant increase in insulin levels following consumption of 5 and 10 g D-ribose was accompanied by a decrease in serum blood glucose levels, the comparison between the two parameters was not statistically significant. Mean insulin levels were significantly greater in the 40- to 50-year-old group compared to the 24- to 30-year-old group. Baseline uric acid levels were within normal ranges in all subjects. Levels of uric acid in the 5 and 10 g groups were significantly higher then the uric acid levels of the 2 g group at 30 and 60 minutes (328 ± 0.9 and 318 ± 0.9 *vs.* 297 ± 0.1 μM; time of measurement not specified). The baseline lactate levels were reported to be within the normal range for all subjects, and no significant differences were observed between doses, time points for a specific dose, or age of the subject at a specific dose. However, higher lactate levels were observed in the younger subjects at 60 and 120 minutes following D-ribose ingestion compared to the older subjects, and a decrease in lactate levels over time was also reported. Although there was a trend, differences in lactate levels between doses, time points per treatment, and age per treatment were not statistically significant. No significant differences were observed in the rate of carbohydrate oxidation between age groups, time points, dose levels, dose levels at specific time points, age groups at specific doses, or age groups at specific time points.

The authors stated that the increase in uric acid levels may have resulted from D-ribose-induced purine synthesis, as uric acid is a catabolic end product of adenosine and inosine. Based on the lack of significant changes in lactate levels with any dose of D-ribose, the authors concluded that the observed hypoglycemia did not result from increased glycolysis with accompanying increased Krebs cycle activity, since lactate is an end product of glycolysis. They also stated that D-ribose-induced hypoglycemia at the 10 g dose did not occur because of an increase in

glucose oxidation since the rate of carbohydrate oxidation did not significantly change following D-ribose ingestion. It was concluded that bolus oral doses of D-ribose at levels up to 10 g were well tolerated without adverse effects.

The effects of intravenous (i.v.) D-ribose on blood glucose levels have been studied in a randomized, double-blind, placebo-controlled crossover study. Subjects with cardiomyopathy (22 men, 3 women, mean age of 57 ± 11 years) were administered D-ribose (provided by Bioenergy) dissolved in water (180 mg/kg body weight/hour) or placebo (1.8 mL/kg body weight/hour of 5% w/v dextrose [glucose] dissolved in water) by i.v. infusion for 4 hours following an 8 hour fast (Sawada *et al.*, 1999). A 5% glucose solution was administered concomitantly with D-ribose at a rate of 100 mL/hour, providing 20 g glucose in total (assuming 70 kg body weight). The D-ribose infusion provided approximately 50.4 g D-ribose and the placebo infusion provided approximately 25.2 g glucose in total. In the second phase of the study, subjects were crossed over to the alternate test article using study procedures that were identical to those of the first day. Blood glucose measurements were performed at the beginning and end of each 4-hour period. Complete data were reported for 21 subjects. Information about medical diagnoses or medications was not provided; however, the available fasting blood glucose values were within the diabetic range (>126 mg/dl) in one subject, within the impaired fasting glucose range (100 to 126 mg/dl) in 7 subjects, and within the normal range for the remaining subjects. No significant changes in blood glucose levels were reported at the end of D-ribose infusion compared to baseline (105.3 ± 27.0 *vs.* 98.5 ± 16.2 mg/dl), nor were there differences between placebo and D-ribose treatments following infusion (117.2 ± 27.4 *vs.* 105.3 ± 27.0 mg/dl). Results were not affected by the order of treatment (D-ribose infusion on Day 1 *versus* placebo infusion on Day 1). These results indicate that the blood glucose-lowering effects of D-ribose when provided alone were ameliorated by concurrent administration of glucose.

Additional clinical and case studies conducted on D-ribose manufactured by Bioenergy or from other sources are described in Table 3. Results from these studies indicate that oral D-ribose administration is well tolerated at doses of up to 60 g per day (approximately 0.9 g/kg body weight). Clinical adverse events were minimal with episodes of diarrhea at bolus doses of greater than 60 g. These doses are more than 8 times higher than the estimated 90th percentile intake of D-ribose from the proposed food uses. Studies involving bolus oral or i.v. doses of 10 g D-ribose or greater were associated with significant decreases in blood glucose levels. In these studies, subjects were given a bolus dose of D-ribose formulations containing no added energy source following an overnight fast. The reduction in blood glucose levels following bolus administration was shown to be clinically asymptomatic and transient, with levels returning to baseline at approximately 2 hours.

When D-ribose was infused concurrently with an additional carbohydrate source of energy, (glucose), no significant decreases in blood glucose levels were observed (Sawada *et al.*, 1999). Although Sawada *et al.* (1999) did not assess blood glucose levels following D-ribose

administration alone, a decrease of 25% would be expected based on the findings of Gross and Zollner (1991). In this study, D-ribose administered orally or *via* i.v. infusion over 4 to 5 hours, providing approximately 58 g D-ribose in total, resulted in a 25% decrease in serum glucose levels at the end of the treatment period compared to baseline levels (Gross and Zollner, 1991). Therefore, based on the results of Sawada *et al.* (1999) and Gross and Zollner (1991), 20 g glucose is sufficient to maintain normal blood glucose levels when administered concurrently with 50 g D-ribose (assuming a linear dose-response relationship, 0.4 g glucose would be needed for 1 g D-ribose), which indicates that co-administration of glucose with D-ribose will ameliorate any decrease in blood glucose levels noted from previous acute studies in which D-ribose was administered alone.

Under the conditions of intended use, D-ribose would be included as an ingredient in food and beverage products with additional sources of energy in the form of carbohydrate that would likely provide sufficient amounts of glucose to ameliorate the blood glucose lowering effects of D-ribose. For example, given an average volume of 24 fluid ounces (approximately 710 mL) and a 2.2% proposed use-level for D-ribose, a sports drink would contain approximately 15.6 g D-ribose. To prevent the decrease in blood glucose levels caused by D-ribose alone, approximately 6.2 g glucose would be required (assuming 0.4 g glucose is needed for 1 g D-ribose). Sports drinks contain on average 15 g sugar per serving, which is considered more than enough to compensate for the potential decrease in blood glucose levels caused by D-ribose. Although low-calorie beverages will not provide additional sources of energy, these beverages will contain less than 3 g D-ribose (0.4% [proposed use-level of D-ribose] x 710 mL [average beverage volume]), which is below the level that has been shown to result in a significant reduction in blood glucose.

While statistically significant decreases in blood glucose levels were apparent with bolus doses of 10 g or greater, no statistically significant differences were reported following a bolus dose of 5 g or less. Furthermore, no significant effects on blood glucose levels were reported when D-ribose was provided with meals at a daily dose of 20 g in divided doses for 14 days (Seifert *et al.,* 2001), or when D-ribose was co-administered by i.v. infusion with lesser amounts of glucose (Sawada *et al.*, 1999).

The lack of clinical hypoglycemic symptoms following bolus doses may be due to an increase in ATP production resulting from D-ribose consumption, providing a source of energy in conditions of decreased glucose levels. Support for this mechanism is provided in several studies, including animal experiments which have shown that D-ribose increases ATP production after intense muscle contractions or myocardial infarction (Zimmer *et al.,* 1989; Zarzeczny *et al.*, 2001). Hellsten *et al.* (2004) demonstrated that during recovery after intense exercise, muscle ATP levels were fully restored to pre-exercise levels in human subjects who received oral D-ribose prior to exercise, and were higher in those who received D-ribose compared to those who received placebo, indicating that D-ribose contributes to the resynthesis of ATP levels following exercise. In addition, the increase in ATP levels may also affect glycogenolysis, as the

enzyme glycogen phosphorylase, which catalyzes the breakdown of glycogen to glucose-1-phosphate, is inhibited by high concentrations of ATP. Additionally, the reduction in blood glucose levels may have resulted from the competitive effect of D-ribose on the enzyme phosphoglucomutase, which is involved in glycogenolysis. Thus, by increasing levels of ATP or by successfully competing for enzymes involved in glycogen breakdown, D-ribose may reduce blood glucose levels by reducing glycogenolysis.

Increased insulin levels may have also contributed to the acute changes in blood glucose levels, as decreases in blood glucose were often associated with a slight but transient increase in insulin secretion, although results from clinical studies indicated that changes in glucose levels could not be explained fully by the increased insulin levels. Furthermore, the decreases in blood glucose levels did not result from changes in glucose oxidation or increases in glycolysis.

Although a significant increase in uric acid levels was reported in some studies, the response was not dose-dependent, as uric acid levels following ingestion of 10 g D-ribose were lower than those after a 5 g dose (Fenstad *et al.*, 2000 ; Frelich and Seifert, 2001 [abstract]). Furthermore, the values reported in most of the studies were within the normal range for adult males and females (3.6 to 7.7 and 2.5 to 6.8 mg/dl, respectively) (Murray *et al.*, 2000). Pliml *et al.* (1992) reported values outside the normal range, but the dose of D-ribose was high (60 g/day) and this study was conducted in subjects with severe coronary artery disease.

Bioenergy's D-ribose is sold in large quantities for use in a variety of nutritional products. From October 1, 2002 to March 31, 2007, approximately 440 metric tonnes of D-ribose were sold. Of that amount, approximately 30 metric tonnes were sold for use in products that specifically target cardiovascular and skeletal muscle health and wellness. The recommended dosage for these uses is 5 g, twice per day. Bioenergy directly supplied over 17,000 individuals, and approximately 25,000 additional individuals have received these products directly from third party suppliers, including approximately 5,000 physicians and clinics.

Bioenergy has not received any reports of adverse events including symptoms of hypoglycemia from individuals consuming D-ribose. Occasional nervousness or lightheadedness for a period of time after taking a 5 g dose has been reported, but in each case it was the result of taking a dose on an empty stomach and dissolved in water with no accompanying food or nutrients. No cases involving fainting or symptoms requiring medical attention have been reported. Additionally, there have been no reports of loose stools.

Summary

D-ribose is a 5-carbon sugar that occurs endogenously in all cells of the human body. It is a structural component of genetic material and numerous intracellular metabolic reactions, and its phosphate forms have been detected in numerous human and animal cells and tissues. It is produced endogenously in the human body at levels similar to or higher than the estimated daily intake of D-ribose from the proposed food uses (approximately 3 to 19 g/day *versus* up to

7.24 g/day). Metabolic data indicate that D-ribose is converted to ribose 5-phosphate, which enters the pentose phosphate pathway, producing glucose, or is used to synthesize nucleic acids and ATP. Glucose, a ubiquitous sugar that is a metabolic product of many dietary carbohydrates, is utilized by well-characterized metabolic pathways, eventually yielding ATP, CO_2 and water.

The safety of D-ribose is further supported through metabolism studies which show that D-ribose is primarily used by tissues to initiate purine and pyrimidine biosynthesis, with unused pentose phosphates converted to glycolytic intermediates and glucose, which is a constituent and/or metabolic product of dietary carbohydrates. Safety is confirmed through animal studies (90-day and reproductive toxicity studies in rats) conducted with D-ribose manufactured by Bioenergy. In the 90-day study, a number of parameters in D-ribose-treated animals, such as body weight and organ weights (including cecal weight) were reported to be significantly different from control. However, these effects were attributed to the excessive dietary concentrations of carbohydrate and thus were considered a physiological rather than a toxicological response. Therefore, the NOAEL was considered to be 15 g/kg body weight/day, the highest dose tested. Likewise, similar physiological adaptive responses were noted in the reproductive toxicity study, as well as some skeletal anomalies and variations that were described as reversible and previously reported in the rat strain used in the study.

A number of human clinical trials of differing design and dosages have been conducted with D-ribose. Overall, D-ribose has been shown to be well tolerated with no adverse events reported other than diarrhea at doses in excess of 60 g/day. Bolus doses of 10 g or greater have resulted in asymptomatic decreases in blood glucose; however, these effects were reported in subjects who were given bolus doses of D-ribose formulations only without other added carbohydrate sources of energy after an overnight fast. Food and beverage products containing D-ribose will also contain other energy sources with the exception of low-calorie beverages. However, because the proposed use-level for D-ribose in low-calorie beverages is 0.4%, these beverages will only contain approximately 2.8 g D-ribose (assuming a 710 mL beverage), which does not result in a significant decrease in blood glucose.

Changes in blood glucose levels were clearly reported as being asymptomatic, which may be explained by elevated ATP levels that have been demonstrated in several animal and clinical studies following D-ribose consumption. Increased insulin levels following D-ribose administration, as well as a slowing of glycogenolysis by D-ribose or by increased ATP levels, may have contributed to the observed reduction in blood glucose levels. While significant decreases in blood glucose levels were noted following high bolus doses after an overnight fast, no significant changes were reported following daily dosages of 20 g in divided doses for 14 days when administered with food. Furthermore, blood glucose levels were not significantly altered when 20 g D-ribose was concurrently administered with approximately 50 g D-ribose by i.v. infusion, indicating that co-administration of an additional carbohydrate source of energy will ameliorate the drop in blood glucose that occurs when D-ribose is given alone.

The lack of any toxicologically significant findings in the pre-clinical studies at dosages of approximately 15 g/kg body weight/day coupled with the lack of adverse events in human studies at dosages of 20 g/day for 14 days support the conclusion that D-ribose is safe for its intended use in food at 90th percentile all-user intakes of up to 7.24 g D-ribose/day. This is corroborated by post-marketing surveillance indicating that Bioenergy's D-ribose has been consumed by over 42,000 individuals at daily recommended doses of 10 g with no reports of hypoglycemia symptoms or adverse events requiring medical attention. Furthermore, FDA raised no questions in response to 2 pre-notifications for D-ribose (manufactured by Bioenergy) as an NDI for use as a dietary supplement at doses up to 20 g/day.

The data and information contained in this report support the conclusion that the intake of D-ribose would not be expected to cause adverse effects in humans under the conditions of its intended use in food.

Conclusion

Based on critical, independent, and collective evaluation of the available data and information summarized above, we conclude that the proposed uses of D-ribose, meeting appropriate food grade specifications and manufactured in compliance with current Good Manufacturing Practice, in beverages and beverage bases (calorie-reduced non-cola carbonated beverages, non-cola carbonated beverages, non milk-based meal replacements, sports, isotonic, and energy drinks), coffee and tea (instant tea, specialty and spiced teas), frozen dairy desserts and mixes (frozen yogurt, ice cream and frozen milk desserts (excluding novelties)), grain products and pasta (energy and meal replacement bars), hard candy (selected hard candy), milk products (milk-based meal replacements, milk drinks (no malts or shakes), yogurts), processed fruits and fruit juices (calorie-reduced fruit drinks and ades, fruit juices, fruit nectars), processed vegetables and vegetable juices (vegetable juice) and soft candy (selected soft candy (excluding chocolate bars)), at the levels indicated herein, are safe .

We further conclude that these proposed uses are Generally Recognized as Safe (GRAS) based on scientific procedures.

It is our opinion that other qualified experts would concur with these conclusions.

Prof. James W. Anderson, M.D. University of Kentucky	13 December 2007 Date
Prof. Joseph F. Borzelleca, Ph.D. Virginia Commonwealth University, Medical College of Virginia	13 December 2007 Date
Prof. Robert Nicolosi, Ph.D. University of Massachusetts Lowell	20 December 2007 Date

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Table 1 Chemical and Physical Specifications for D-Ribose		
Specification Parameter	**Specification**	**Method of Analysis**
Appearance	Dry shape-holding characteristics with powdery texture that is white to slightly yellow in color.	Internal method (SOP-QC002-00)
Melting point	80 to 90°C	Internal method (derived from method I, CP2005 Appendix VI C)
Specific rotation	-19.0 to -21.0°	CP2005 Appendix VI E
D-ribose (purity)	97.0-103.0%	Internal method (SOP-QC002-00)
Loss on drying (moisture)	<2.0%	Internal method (derived from method I, CP2005 Appendix VIII L)
Ash	≤0.2%	CP2005 Appendix VIII N
Clarity of solution	≥95% transmittance	Bioenergy 30-014
Lead	≤0.1 ppm	AOAC 993.14
Arsenic	≤1 ppm	Method I, CP2005 Appendix VIII J
Total plate count	NMT 100 CFU/g	AOAC 990.12
Salmonella sp.	Negative/25g	AOAC 991.14
Coliforms	NMT 10 CFU/g	AOAC 992.21
Yeast and mold	NMT100 CFU/g	AOAC 992.11

Table 2 Summary of the Individual Proposed Food Uses and Use-Levels for D-Ribose in the U.S.

Food Category	Proposed Food Use	Use-level (%)	D-Ribose per Serving Size (g/serving)
Beverages and Beverage Bases	Calorie-Reduced Carbonated Beverages, Non-Cola	0.4	0.96
	Carbonated Beverages, Non-Cola	0.4	0.96
	Meal Replacements, Non-Milk-Based	0.4	0.96
	Sports, Isotonic, and Sports Drinks	2.2	5.28
Coffee and Tea	Instant Tea	0.7	1.68
	Specialty and Spiced Teas	0.7	1.68
Frozen Dairy Desserts and Mixes	Frozen Yogurt	2.2	4.95
	Ice Cream and Frozen Milk Desserts (Excluding Frozen Novelties)	0.4	0.34
Grain Products and Pasta	Energy and Meal Replacement Bars	5.0	2.00
Hard Candy	Selected Hard Candy	2.0	0.25
Milk Products	Milk-Based Meal Replacements	1.0	2.40
	Milk Drinks (No Malts or Shakes)	0.4	0.96
	Yogurt	2.2	4.95
Processed Fruits and Fruit Juices	Calorie-reduced Fruit Drinks and Ades	0.4	0.96
	Fruit Juice	1.2	2.88
	Fruit Nectars	1.0	2.40
Processed Vegetables and Vegetable Juices	Vegetable Juice	1.0	2.40
Soft Candy	Selected Soft Candy (Excluding Chocolate Bars)	1.67	0.69

Table 3 Summary of Human Studies for D-Ribose (Oral Administration)

Study Population	Duration	Dose*	End-points Measured	Results	Reference
Studies Conducted on Bioenergy's D-Ribose					
21 healthy, non-diabetic subjects (12 ♂, 7 ♀)	14 days	10 g, 2x/day	CBC, albumin, ALK P, GGT, ALT, AST, uric acid, glucose	↑ AST and uric acid at day 7 and ↓ at day 14; ↓ WBC in ♀ and ↑ in ♂; ↑ ALK P in ♀; ↓ GGT at day 7 but return to baseline at day 14 No adverse physical symptoms	Seifert *et al.*, 2001; Seifert *et al.*, 2001 [abstract]
10 healthy, non-diabetic males	Single dose	2, 5 or 10 g, 4-11 days between each tested dose	Glucose, insulin, uric acid, lactate, oxygen uptake	↓ glucose at 10 g dose that returned to baseline at 2 h; ↑ uric acid No significant ↓ in glucose following 2 or 5 g D-ribose No adverse effects	Fenstad *et al.*, 2000; Frelich and Seifert, 2001 [abstract]
19 healthy male subjects, aged18-35 years (12 completed the study)	4 weeks	10 g/day, divided into 2 doses	Body composition and exercise performance	No adverse events (diarrhea, gastrointestinal distress, or muscle cramping) were reported	Van Gammeren *et al.*, 2002
8 healthy male subjects, average age of 25 ± 1.3 years	3 days Subjects underwent exercise training for 7 days ("training") followed by 3 days of D-ribose administration and a training session 72 h after the last training session ("72-h test")	200 mg/kg bw, 9 doses in total, given after exercise training (126 g total)	Plasma glucose, insulin and urate	↓ glucose compared to placebo during recovery after the 72-h test, and at 60 and 90 minutes after the 72-h test compared to levels immediately after the 72-h test (maximal ↓ of 25%), but return to baseline at 2 h ↑ insulin at 30 minutes after the 72-h test compared to levels at rest, but return to baseline at 60 minutes ↑ urate in the 72-h test compared to levels immediately after training, and compared to placebo at 10 minutes after the 72-h test	Hellsten *et al.*, 2004
15 CAD patients with CHF (14 ♂, 1 ♀)	3 weeks	5 g, 3x/day	Quality of life (questionnaire), physical function and diastolic function tests	No adverse effects in exercise testing; significant improvement in overall score of quality of life Improvement in physical function and diastolic function	Omran *et al.*, 2003

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Table 3 Summary of Human Studies for D-Ribose (Oral Administration)

Study Population	Duration	Dose*	End-points Measured	Results	Reference
41 Fibromyalgia and/or chronic fatigue syndrome patients (of the 36 who completed the study, 8♂, 28 ♀)	Average 28 days	5 g/ 3x/day	Symptoms of fibromyalgia and chronic fatigue syndrome Patients were asked if any adverse effects occurred during treatment	D-Ribose was well-tolerated. Five patients were excluded because of non-compliance. Of these patients, 3 withdrew from D-ribose treatment because of a hyperanxious feeling (1), lightheadness (1), and increased appetite (1). The other 2 patients did not begin treatment. Of the patients who completed the study, 1 reported transient nausea and 1 reported mild anxiety. Both reactions were reversed by dose reduction.	Teitelbaum *et al.*, 2006
1 ♀ Fibromyalgia patient	2 months	5 g, 2x/ day	Symptoms of fibromyalgia	No adverse effects	Gebhart and Jorgenson, 2004
Studies Conducted on D-Ribose from Other Sources					
9 healthy subjects (8 ♂, 1 ♀)	1 day	166.7 mg/kg bw/h in 5-minute increments for 5 h (58 g total), or 83.3 mg/kg bw/h for 5 h followed by 166.7 mg/kg bw/h for 5 h (87 g total)	Serum glucose, insulin, c-peptide	↓ glucose (26%) and ↑ insulin at 166.7 mg/kg bw/h dose during treatment, but measurements were not taken after treatment was stopped, and insulin levels remained within normal ranges. No symptoms of hypoglycemia were reported.	Gross and Zöllner, 1991
10 healthy subjects (9 ♂, 1 ♀)	Single dose	0.5 g/kg bw (oral: consumed over 35 min; i.v.: 35-min infusion) (35 g total)	Oral: plasma insulin i.v.: plasma insulin and glucose	Oral: Slight ↑ in insulin at 15 min, peaked at 20 min (2x baseline levels) followed by a rapid ↓ i.v.: ↓ glucose (remained within 85% of control values), transient ↑ in insulin No symptoms of hypoglycemia were reported.	Goodman and Goetz, 1970

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Table 3 Summary of Human Studies for D-Ribose (Oral Administration)

Study Population	Duration	Dose*	End-points Measured	Results	Reference
8 healthy subjects (7 ♂, 1 ♀) and 5 MAD-deficient patients (3 ♂, 2 ♀)	1 day	Up to 200 mg/kg bw/h x 5 h (70 g total)	Serum glucose, heart rate, blood pressure, serum uric acid concentrations and clearance, creatinine clearance, bilirubin	↓ glucose (28%) during treatment, but levels were not measured after treatment was stopped Treatment generally well tolerated; hyperperistalsis in most healthy subjects; doses of 200 mg/kg bw/h resulted in diarrhea	Gross *et al.*, 1989
10 healthy adults	Single dose	1 g/kg bw (70 g total)	Blood glucose, plasma insulin, human growth hormone, serum free fatty acid	↓ glucose (38%); ↑ insulin; ↓ free fatty acid; measured up to 3 h post-consumption Headache reported by 1 subject, peristalsis and borborygmi observed in 1 subject, diarrhea reported in 2 subjects	Ginsburg *et al.*, 1970
13 normal subjects (7 ♂, 6 ♀), 6 probable diabetics (2 ♂, 4 ♀), and 15 diabetics (4 ♂, 11 ♀)	Single dose	15 g	Serum glucose, serum insulin	↓ glucose (maximal decrease of 27% in normal subjects), reaching a nadir at 60 min. post-administration and returning toward baseline levels at 120 min. Blood glucose lowering response was less pronounced in diabetics compared to normal subjects. No significant changes in insulin levels	Steinberg *et al.*, 1970
20 ♂ CAD patients	3 days	15 g, 4 x/day	Serum uric acid levels, aminotransferase and gammaglutamyl transpeptidase activities Time to angina and time to ST depression during treadmill exercise	↑ uric acid in 3 patients; ↑ aminotransferase and gammaglutamyl transpeptidase activities in 2 patients Treatment generally well tolerated, with no symptoms typical of hypoglycemia ↑ time to moderate angina and time to ST depression versus baseline	Pliml *et al.*, 1992
5 McArdle's disease patients (4 ♂, 1♀)	7 days	15 g, 4 x/day after meals	Lactate, free fatty acids, glycerol, β-hydroxybutyrate, ammonia, pH, potassium, creatine kinase	1 patient reported diarrhea, 1 described occasional symptoms of hypoglycemia, 1 reported light-headedness and hunger	Steele *et al.*, 1996
1 ♂ MAD-deficient patient	Not disclosed	50-60 g/day divided into 12-15 doses	Monthly blood cell counts, peripheral blood smears	No abnormalities of leukocytes; no symptoms of hypoglycemia No side effects, although single doses of >20 g resulted in diarrhea	Zöllner *et al.*, 1986

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Table 3 Summary of Human Studies for D-Ribose (Oral Administration)

Study Population	Duration	Dose*	End-points Measured	Results	Reference
1 ♀ ASase-deficient patient	3 months	40 g/day divided in 4-10 doses	Uric acid excretion, urinary succinylnucleoside, urate, glucose levels	↑ uric acid excretion and urate levels; ↓ glucose levels No toxicity, but doses of up to 100 g/day resulted in mild diarrhea	Salerno *et al.*, 1998
1 ♀ ASase-deficient patient and healthy adult volunteers (number, age, sex not disclosed)	ASase-patient:: several months Healthy volunteers: not disclosed	ASase-deficient patient: 10 mmol/kg bw/day (46.5 g/day) Healthy volunteers: Up to 30 mmol/kg bw/day (270 g/day), divided into 4 doses.	Uric acid, urinary urate-to-creatinine ratio, serum glucose In the ASase-deficient patient, hematological parameters and liver enzymes were also measured	ASase-deficient patient: ↑ urate-to-creatinine ratio and urate levels; ↓ glucose levels No changes in liver enzymes and in hematological parameters No appreciable toxic effects, although higher doses (up to 20 mmol/kg bw/day) caused mild diarrhea, which was reversed by reducing the dose Healthy volunteers: 13 mmol/kg bw/day (117 g/day): 10-20% decrease in serum glucose, 2 to 3-fold increase in urate and urinary urate-to-creatinine ratio (values not provided) D-Ribose was tolerated without complaints, with the exception of occasional diarrhea at higher doses	Salerno *et al.*, 1999

Abbreviations: ↑, increased, ↓, decreased, ALK P, alkaline phosphatase; ASase, adenylosuccinase, AST, alanine aminotransferase; bw, body weight; CAD, coronary artery disease, CBC, complete blood count; CHF, congestive heart failure; GGT, gamma glutamyltransferase; MAD, myoadenylate deaminase; WBC, white blood cell.
Unless indicated, D-ribose was dissolved in water and given to subjects after an overnight fast.

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Attachment 1

Attachment 1

Curricula Vitae

Curriculum Vitae
JAMES W. ANDERSON, MD
University of Kentucky
Metabolic Research Group

PLACE AND DATE
OF BIRTH:

FAMILY:

EDUCATION:	1958	B.A. West Virginia University
	1961	M.D. Northwestern University
	1965	M.S. Mayo Graduate School
TRAINING:	1961-62	Internship, Presbyterian Hospital, Denver, Colorado
	1962-65	Fellow in Medicine and Endocrinology Mayo Clinic, Rochester, Minnesota
MILITARY:	1965-68	U.S. Army (Captain), Denver, Colorado Chief, Metabolic-Renal Section, Research Endocrinologist, Nutrition Research Laboratory, Fitzsimons Hospital

FACULTY APPOINTMENTS:

2003-present	WOC Employee, VA Medical Center Lexington, Kentucky
1978-present	Professor of Medicine University of Kentucky College of Medicine
1978-present	Professor of Clinical Nutrition University of Kentucky, Lexington, Kentucky
1985-present	Medical Director, HMR Fasting Program, University of Kentucky, Lexington, Kentucky
1973-03	Chief, Endocrine-Metabolic Section VA Medical Center, Lexington, Kentucky
1983-84	Visiting Scientist, Massachusetts Institute of Technology Cambridge, Massachusetts
1980-83	Chief, Medical Service VA Medical Center, Lexington, Kentucky
1973-78	Associate Professor of Medicine University of Kentucky College of Medicine Lexington Kentucky
1968-73	Assistant Professor of Medicine University of California Medical School San Francisco, California

AWARDS:	2004	Seale Harris Award for Excellence in Endocrinology Research, Southern Medical Association
	2002	Vahouny Medal for Excellence in Dietary Fiber Research

CERTIFICATION AND LICENSE:

1975	American Board Internal Medicine
1973	Kentucky

PROFESSIONAL ORGANIZATIONS:

Alpha Omega Alpha
American College of Nutrition - Fellow
American College of Physicians - Fellow
American Diabetes Association
American Federation for Clinical Research
American Society for Clinical Nutrition
Endocrine Society
Obesity Research Network
Society for Experimental Biology and Medicine

EDITORIAL BOARD:

1997-present	Vegetarian Nutrition
1991-97	Medicine, Exercise, Nutrition and Health
1987-present	Diabetes: Self-Management
1989-2004	Prevention
1974-77	American Journal of Clinical Nutrition

REVIEWER:

American Journal of Clinical Nutrition
Diabetes
Diabetes Care
Diabetologia
European Journal of Clinical Nutrition
International Journal of Obesity
Journal of the American Medical Association
Journal of Nutrition
Journal of American College of Nutrition
Journal of American Dietetic Association
Metabolism
New England Journal of Medicine

EDITOR:	1979-96	HCF Nutrition Newsletter (Circulation 10,000)

PROFESSIONAL SERVICE:

2000-present	Obesity Research Network, Chairman of the Board and President
2003-2006	Executive Council, VA Weight Management/ Physical Activity
2000-2003	American College of Nutrition, Secretary, Vice President, President-Elect

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1974-2005	Director, Metabolic Research Group
1996-present	Obesity Research Network; Co-Founder & Coordinator
1997-00	American College of Nutrition, Board of Directors

GRANTS AS PRINCIPAL INVESTIGATOR:

2000-2004	VA Cooperative Study #465, Glycemic Control and Complications in Diabetes Mellitus Type 2 VADT (VA Diabetes Trial) 85 to be enrolled
2000-2004	NIH - R21 Program Project, "Soy protein in early diabetic nephropathy" -
2000-02	Bupropion SR Obesity Study. PI for 6 Site Study Sponsor: Glaxo-Wellcome
1974-2005	University of Kentucky Diabetes Research Fund Grants from Foundations, Corporations and Individuals, (1995-2004)

TEACHING:

Undergraduate

1973-2004	Ward teaching attending 20 weeks per year (average) Four formal lectures per year

Graduate

1973-2004	Ward teaching attending 20 weeks per year (average) Four to six conferences per year

Postgraduate

1974-2003	Annual Endocrine Conference (UK) (postgraduate)
1975-present	Chair, yearly, of one or two national or international workshops on nutrition, diabetes, dyslipidemia or obesity
1990-present	Major advisor: 6 PhD Candidates; 4 MS Candidates

PUBLIC SERVICE:

2003-present	Board of Trustees, Georgetown College, Georgetown, Kentucky
1996-2004	Downtown Christian Unity Taskforce
1994-96	Chairman, Board of Trustees, Georgetown College, Georgetown, Kentucky
1989-96	Board of Trustees, Georgetown College, Georgetown, Kentucky
1974-present	Deacon, Sunday School Teacher, Calvary Baptist Church

PUBLICATIONS, REFEREED JOURNALS:

1. Anderson JW, Kilbourn KG, Robinson J, and Wright PH. Diabetic acidosis in rats treated with anti-insulin serum. Clin Sci 24:417-430, 1963.

2. Anderson JW, Sawyer KC Jr, Sheridan DP. Cystic fibrosis of the pancreas with diabetes mellitus. Rocky Mountain Med J 60:32-35, 1963.

3. Anderson JW, McConahey WM, Alarcon-Segovia D, Emslander RF, Wakim KG. Diagnostic value of thyroid antibodies. J Clin Endocrinol Metab 27:937-944, 1967.

4. Anderson JW. Hyperglycemic diabetic stupor: A spectrum of disorders. Mil Med 133:538-542, 1968.

5. Anderson JW, Herman RH. Classification of reactive hypoglycemia. Am J Clin Nutr 22:646-650, 1969.

6. Gorman CA, Anderson JW, Flock EV, Owen CA Jr, Wakim KG. Effect of experimentally induced thyroiditis on biosynthesis of thyroxine in rats. Acta Endocrinol 62:11-20, 1969.

7. Pastore RA, Anderson JW, Herman RH. Anterior and posterior hypopituitarism associated with sickle cell trait. Ann Intern Med 71:593-598, 1969.

8. Anderson JW, Wakim KG, McConahey WM. The influence of experimental thyroiditis on thyroid function. Mayo Clinic Proc 44:711-724, 1969.

9. Anderson JW, Herman RH, Newcomer KL. Improvement of glucose tolerance of fasting obese patients given oral potassium. Am J Clin Nutr 22:1589:1596, 1969.

10. Anderson JW, Zakim D. The influence of alloxan-diabetes and fasting on glycolytic and gluconeogenic enzyme activities of rat intestinal mucosa and liver. Biochem Biophys Acta 201:236-241, 1970.

11. Anderson JW. Pyruvate carboxylase and phosphoenolpyruvate carboxykinase in rat intestinal mucosa. Biochem Biophys Acta 208:165-167, 1970.

12. Everett ED, Newcomer KL, Anderson JW, Bergin J, Overholdt EL. Goodpasture's syndrome. Response to mercaptopurine and prednisone. JAMA 213:1849-1852, 1970.

13. Anderson JW, Herman RH. Treatment of reactive hypoglycemia and sulfonylureas. Am J Med Sci 261:16-23, 1971.

14. Ho W, Anderson JW. Phosphofructokinase in rat jejunal mucosa: Subcellular distribution, isolation, and characterization. Biochem Biophys Acta 227:354-363, 1971.

15. Anderson JW, Herman RH, Tyrrell JB, Cohen RB. Hexokinase: A compartmented enzyme. Am J Clin Nutr 24:642-650, 1971.

16. Tyrrell JB, Anderson JW. Glycolytic and pentose phosphate pathway enzymes in jejunal mucosa, adaptive responses to alloxan diabetes and fasting in the rat. Endocrinology 89:1178-1185, 1971.

17. Anderson JW, Herman RH. Effect of fasting, caloric restriction and refeeding on glucose tolerance of normal men. Am J Clin Nutr 25:41-52, 1972.

18. Anderson JW, Stowring L. Glycolytic and gluconeogenic enzyme activities in renal cortex of diabetic rats. Am J Physiol 224:930-936, 1973.

19. Anderson JW, Rosendall AF. Gluconeogenesis in jejunal mucosa of guinea pig. Biochem Biophys Acta 304:384-388, 1973.

20. Anderson JW, Herman RH, Zakim D. Effect of high glucose and high sucrose diets on glucose tolerance of normal men. Am J Clin Nutr 26:600-607, 1973.

21. Anderson JW, Tyrrell JB. Hexokinase activity of rat intestinal mucosa: Demonstration of four isozymes and changes in subcellular distribution with fasting and refeeding. Gastroenterology 65:69-76, 1973.

22. Murphy ED, Anderson JW. Tissue glycolytic and glucoenogenic enzyme activities in mildly and moderately diabetic rats, influence of tolbutamide administration. Endocrinology 94:27-34, 1974.

23. Anderson JW. Glucose metabolism in jejunal mucosa of fed, fasted, and streptozotocin-diabetic rats. Am J Physiol 226-229, 1974.

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25. Anderson JW. Endocrine manifestations of lung tumors. J Ky Med Assoc 72:208-211, 1974.

26. Anderson JW. Alterations in metabolic fate of glucose in the liver of diabetic animals. Am J Clin Nutr 27:746-755, 1974.

27. Anderson JW. Metabolic abnormalities contributing to diabetic complications. I. Glucose metabolism in insulin-insensitive pathways. Am J Clin Nutr 28:273-280, 1975.

28. Anderson JW, King P. Subcellular distribution of hexokinase activity in rat jejunal mucosa: Response to diabetes and dietary changes. Biochem Med 12:1-11, 1975.

29. Anderson JW, Herman RH. Effects of carbohydrate restriction on glucose tolerance of normal men and reactive hypoglycemic patients. Am J Clin Nutr 28:748-755, 1975.

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33. Kiehm TG, Anderson JW, Ward K. Beneficial effects of a high-carbohydrate high-fiber diet on hyperglycemic diabetic men. Am J Clin Nutr 29:895-899, 1976.

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23. Anderson JW. Plant fiber: Dietary effects on glucose and lipid metabolism. Proc Fourth International Conference on Human Functioning, Wichita, KS, 1981.

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39. Anderson JW. Dietary fiber and diabetes: An update. In: Jansen GR, ed. Proceedings 1985, Lillian F. Smith Conference, Ft. Collins, CO, Colorado State University, 1985.

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104. Anderson JW. Cholesterol-lowering effects of soluble fiber in humans. In: Kritchevsky D, Bonfield C, eds. Dietary Fiber in Health and Disease. St. Paul: Eagan Press, 126-136, 1995.

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136. Anderson, JW. Soja: Salud y Nutritición y Seguridad. ("*Soyfoods: Health, Nutrition and Safety Considerations*") La Alimentacion Latinoamericano Part 2:44-49, 2004.

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146. Stephenson TJ, Anderson JW. Phytoestrogens: Renal effects – diabetic nephropathy. Anderson JJB, ed. Phytoestrogen monograph. Champaign, IL. American Oil Chemical Association. In press.

147. Pasupuleti V, Anderson JW. Nutraceuticals, Glycemic Health and Type 2 Diabetes. Wiley-Blackwell. Ames, IA. In preparation.

Joseph Francis Borzelleca

Educational Background:

B.S. St. Joseph's University, Philadelphia, PA, Major: Biology, Chemistry.

M.S. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA, Major: Pharmacology, Physiology.

Ph.D. School of Graduate Studies, Thomas Jefferson University, Jefferson Medical College, Philadelphia, PA. Major: Pharmacology, Biochemistry.

Academic Appointments

Instructor-Associate: Department of Pharmacology, Medical College of Pennsylvania, 1956-1959.

Assistant Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1959-62 and 1962-1967.

Professor: Department of Pharmacology, Toxicology, Medical College of Virginia, 1967-

Head: Division of Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, 1972-1986.

Professor Emeritus: Pharmacology & Toxicology, Department of Pharmacology, Toxicology, Medical College of Virginia, July 1996 –

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **

American Association for the Advancement of Science

American Chemical Society

American College of Toxicology*

American Society of Pharmacology and Experimental Therapeutics**

(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)

International Society of Regulatory Toxicology and Pharmacology*

(Member of Council)

Sigma XI

Society of Experimental Biology and Medicine*

(Councilor; Program Chairman of Southeastern Section)

Society for Risk Analysis

Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President, Food Safety Specialty Section)

Virginia Academy of Science*

(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI

Board of Scientific and Policy Advisors

American Council on Science and Health

Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board

Environmental Carcinogenesis Reviews, 1981-

Journal of Environmental Pathology, Toxicology and Oncology 1977-

Journal of Environmental Science and Health, 1979-

Journal of the American College of Toxicology, 1982-

Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992

Journal of Applied Toxicology, 1989-

Pharmacology, 1978-

Pharmacology and Drug Development, 1980-

Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

- Food and Drug Administration
- National Institute of Mental Health
- National Cancer Institute
- Environmental Protection Agency
- Department of Labor - OSHA (Chairman, Carcinogens Standards Committee)
- U.S. Army - Research and Development Command

Non-Governmental

- National Academy of Sciences - NRC
  - Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
  - Safe Drinking Water Committee
  - Evaluation of Household Substances Committee (1138 Committee)
  - Food Protection Committee
  - Food Additives Survey Committee
  - Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
  - Committee on Risk Assessment of Flame-Retardant Chemicals
- Federation of American Societies of Experimental Biology
  - Select Committee on GRAS Substances
  - Flavors and Extracts
  - Biotechnology Product Safety
  - Caprenin GRAS Committee
- World Health Organization
  - Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)
- NATO/CCMS Drinking Water Committee

Industrial

- Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (11960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)

Planning and participation in continuing education program
(Schools of Dentistry, Medicine and Pharmacy)

Planning and administering each of the three major efforts in pharmacology

(dental, medical, pharmacy) since 1960.

Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Presents lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

Elected senator from the graduate school, then vice-president of the University Senate
Served on various committees (e.g. Curriculum, Search, Animal Care) in each of the four major schools (Dentistry, Graduate, Medical, Pharmacy)

Research

Research was continuously funded from 1956. Sources of support included governmental (U.S.P.H.S.; N.I.H; E.P.A.; N.I.D.A.) and non-governmental (industrial). A list of publications is attached).

Awards

DOD - US Army - Chemical Research Development and Engineering Center

Distinguished Service Award, 1986

National Italian - American Foundation Award

Excellence in Medicine and Community Service, 1987

Thomas Jefferson University

Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences

Outstanding Faculty Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences, Dept. of Pharmacology and Toxicology

Professor of the Year- 1992

American College of Toxicology

Distinguished Service Award- 1997

Virginia's Life Achievement in Science Award- April 2001

2001 Bernard L. Oser Food Ingredient Safety Award by the Institute of Food Technologists

PUBLICATIONS

Borzelleca, J.F. and Manthei, R.W.: Factors influencing pentobarbital sleeping time in mice. Arch. Int. Pharmacodyn. 111:296, 1957.

Borzelleca, J.F.: Studies of the contribution of bladder absorption to the physiological changes induced by pentobarbital. J. Pharm. Exp. Ther 129:305, 1960.

Borzelleca, J.F.: The absorption of nicotine from the urinary bladder of the dog. Arch. Int. Pharmacodyn. 133:444, 1961.

Borzelleca, J.F., Bowman, E.R. and McKennis, H., Jr.: The cardiovascular and respiratory effects of (-)-cotinine. J. Pharmacol. Exp. Ther. 137:313,1962.

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Evaluation of the health aspects of iron and iron salts as food ingredients. 1973.

Evaluation of the health aspects of butylated hydroxytoluene as a food ingredient. 1973.

Evaluation of the health aspects of certain zinc salts as food ingredients. 1973.

Evaluation of the health aspect of pulps as they may migrate to food from packaging materials. 1973.

Evaluation of the health aspects of propylene glycol and propylene glycol monostearate as food ingredients. 1973.

Evaluation of the health aspects of alginates as food ingredients. 1973.

Evaluation of the health aspects of agar-agar as a food ingredient. 1973.

Evaluation of the health aspects of certain red and brown algae as food ingredients. 1973.

Evaluation of the health aspects of cellulose and certain cellulose derivatives of food ingredients. 1973.

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Evaluation of the health aspects of aconitic acid as a food ingredient. 1974.

Evaluation of the health aspects of stannous chloride as a food ingredient. 1974.

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Evaluation of the health aspects of sorbose as a food ingredient. 1974.

Evaluation of the health aspects of sulfuric acid and sulfates as food ingredients. 1974.

Evaluation of the health aspects of potassium iodide, potassium iodate, and calcium iodate as food ingredients. 1975.

Evaluation of the health aspects of dextran as food ingredients. 1975.

Evaluation of the health aspects of calcium oxide and calcium hydroxide as food ingredients. 1975.

Evaluation of the health aspects of succinic acid as a food ingredient. 1975.

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of certain calcium salts as food ingredients. 1975.

Evaluation of the health aspects of glycerin and glycerides as food ingredients 1975

Evaluation of the health aspects of dextrin and corn dextrin as food ingredients. 1975.

Evaluation of the health aspects of sodium thiosulfate as a food ingredient. 1975.

Evaluation of the health aspects of gelatin as a food ingredient. 1975.

Evaluation of the health aspects of bile salts and ox bile extract as food ingredients. 1975.

Evaluation of the health aspects of choline chloride and choline bitartrate as food ingredients. 1975.

Evaluation of the health aspects of aluminum compounds as food ingredients. 1975.

Evaluation of the health aspects of tallow, hydrogenated tallow, stearic acid, and calcium stearate as food ingredients. 1975.

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Evaluation of the health aspects of hydrogenated fish oil as a food ingredient. 1975.

Evaluation of the health aspects of beeswax (yellow or white) as a food ingredient. 1975.

Evaluation of the health aspects of inositol as a food ingredient. 1975.

Evaluation of the health aspects of malic acid as a food ingredient. 1975.

Evaluation of the health aspects of Japan Wax as a substance migrating to food from cotton or cotton fabrics used in dry food packaging. 1976.

Evaluation of the health aspects of carnauba wax as a food ingredient. 1976.

Evaluation of the health aspects of sulfamic acid as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of hydrosulfites as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of gum guaiac as a food ingredient. 1976.

Contributing authorship on the following publications of the Life Science Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of tall oil as it may migrate to foods from packaging materials. 1976

Evaluation of the health aspects of corn sugar (dextrose), corn syrup and invert sugar as food ingredients. 1976.

Evaluation of the health aspects of sucrose as a food ingredient. 1976.

Evaluation of the health aspects of sulfiting agents as food ingredients. 1976.

Evaluation of the health aspects of glycerophosphates as food ingredients. 1976.

Evaluation of the health aspects of magnesium salts as food ingredients. 1976. Evaluation of the health aspects of sodium hydroxide and potassium hydroxide as food ingredients. 1976.

Evaluation of the health aspects of adipic acid as a food ingredient. 1976.

Evaluation of the health aspects of hydrogenated soybean oil as a food ingredient.

Evaluation of the health aspects of formic acid, sodium formate, and ethyl formate as food ingredients. 1976.

Evaluation of the health aspects of lard and lard oil as they may migrate to foods from packaging materials. 1976.

Evaluation of the health aspects of pyridoxine and pyridoxine hydrochloride as food ingredients. 1977.

Evaluation of the health aspects of papain as a food ingredient. 1977.

Evaluation of the health aspects of hypophosphites as food ingredients. 1977.

Evaluation of the health aspects of coconut oil, peanut oil, and oleic acid as they migrate to food from packaging materials, and linoleic acid as a food ingredient. 1977.

Evaluation of the health aspects of pectin and pectinates as food ingredients. 1977.

Evaluation of the health aspects of tannic acid as a food ingredient. 1977.

Evaluation of the health aspects of rennet as a food ingredient. 1977.

Evaluation of the health aspects of acetic acid and sodium acetate as food ingredients. 1977.

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Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of corn silk as a food ingredient. 1977.

Evaluation of the health aspects of bentonite and clay (kaolin) as food ingredients. 1977

Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977.

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Evaluation of the health aspects of calcium pantothenate, sodium pantothenate, and D-pantothenyl acohol as food ingredients. 1978.

Evaluation of the health aspects of Vitamin B12 as a food ingredient. 1978.

Evaluation of the health aspects of Vitamin D2 and Vitamin D3 as food ingredients. 1978.

Evaluation of the health aspects of caffeine as a food ingredient. 1978.

Evaluation of the health aspects of certain glutamates as food ingredients. 1978.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1978.

Evaluation of the health aspects of butylated hydroxyanisole as a food ingredient. 1978.

Evaluation of the health aspects of sodium, potassium, magnesium and zinc gluconates as food ingredients. 1978.

Evaluation of the health aspects of urea as a food ingredient. 1978.

Evaluation of the health aspects of thiamin hydrochloride and thiamin mononitrate as food ingredients. 1978.

Evaluation of the health aspects of biotin as a food ingredient. 1978.

Evaluation of the health aspects of ascorbic acid, sodium ascorbate, calcium ascorbate, erythorbic acid, sodium erythorbate, and ascorbyl palmitate as food ingredients. 1979.

Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients. 1979.

Evaluation of the health aspects of casein, sodium Gaseinate, and calcium caseinate as food ingredients. 1979.

Evaluation of the health aspects of nickel as a food ingredient. 1979

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of soy protein isolates as food ingredients. 1979.

Evaluation of the health aspects of carotene (B-carotene) as a food ingredient. 1979.

Evaluation of the health aspects of nitrogen, helium, propane, n-butane, isobutane, and nitrous oxide as gases used in foods. 1979.

Evaluation of the health aspects of hydrogen peroxide as a food ingredient. 1979.

Evaluation of the health aspects of riboflavin and riboflavin-5-1-phosphate as food ingredients. 1979.

Evaluation of the health aspects of starch and modified starches as food ingredients. 1979.

Evaluation of the health aspects of carbon dioxide as a food ingredient. 1979.

Evaluation of the health aspects of sodium chloride and potassium chloride as food ingredients. 1979.

Evaluation of the health aspects of certain silicates as food ingredients. 1979.

Evaluation of the health aspects of manganous salts as food ingredients. 1979.

Evaluation of the health aspects of copper gluconate, copper sulfate, and cuprous iodide as food ingredients. 1979.

Evaluation of the health aspects of hydrochloric acid as a food ingredient. 1979.

Evaluation of the health aspects of lecithin as a food ingredient. 1979.

Evaluation of the health aspects of potassium acid tartrate, sodium potassium tartrate, sodium tartrate and tartaric acid as food ingredients. 1979.

Evaluation of the health aspects of starter distillate and diacetyl as food ingredients. 1980.

Vitamin A, Vitamin A Acetate, and Vitamin A Palmitate as food ingredients. 1980.

Evaluation of the health aspects of iron and iron salts as food ingredients. 1980.

Evaluation of the health aspects of protein hydrolyzates as food ingredients. 1980.

Evaluation of the health aspects of collagen as a food ingredient. 1981.

Evaluation of the health aspects of methyl polysilicones as food ingredients. 1981

Contributing authorship on the following publications of the Life Sciences Research Office, Federation of American Societies of Experimental Biology (FASEB)

Evaluation of the health aspects of soya fatty acid amines as food ingredients. 1981.

Evaluation of the health aspects of activated carbon (charcoal) as a food processing aid. 1981.

Evaluation of the health aspects of smoke flavoring solutions and smoked yeast flavoring as food ingredients. 1981.

Evaluation of the health aspects of corn mint oil as a food ingredient. 1981.

Evaluation of the health aspects of a mixture. Evaluation of the health aspects of diferrous, dipotassium ferrous, and potassium ferrocyanides as finding agents in wine production. 1981.

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Drinking Water and Health. Safe Drinking Water Committee, Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council, National Academy of Sciences Volume 1, 1977; Volume 2, 1980, Volume 3, 1980 National Academy Press, Washington, D.C.

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EDUCATION

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
St. Anselm's College, New Hampshire	B.A.	1964	Biology
University of New Hampshire, Durham, NH	M.S.	1967	Zoology
University of New Hampshire, Durham, NH	Ph.D.	1971	Zoology-Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE:

1973-74	Post Doctoral Research Fellow, Masonic Medical Research Laboratory, Utica, NY
1973-74	Research Fellow in Nutrition, Harvard School of Public Health, Boston, MA
1973-77	Lecturer, Northeastern University of Boston, MA
1973-78	Research Associate in Nutrition, Harvard School of Public Health, Boston, MA
1977-85	Lecturer in Nutrition, Harvard School of Public Health, Boston, MA
1978-82	Assistant Professor of Comparative Pathology, Harvard Medical School, New England Regional Primate Research Center, Southborough, MA
1982-85	Chairman, Division of Nutrition, Harvard Medical School, New England Regional Primate Research Center, Southborough, MA
1983-85	Visiting Professor, Tufts University School of Nutrition, Medford, MA
1985-	Professor, Department of Clinical Sciences, University of Massachusetts-Lowell, Lowell, MA
1991-	Research Professor of Medicine, University of Massachusetts Medical School, Worcester, MA
1992-	Adjunct Professor, University of Massachusetts Medical School, Worcester, MA
1994-	Director, Center for Health & Disease Research, University of Massachusetts-Lowell, Lowell, MA
1998-03	Coordinator, Office of Collaborative Research, University of Massachusetts Lowell, Lowell, MA
1998-03	Co-Director, Public Health Engineering & Policy Initiative, University of Massachusetts, Lowell, Lowell, MA
1998-03	Special Assistant to the Provost, University of Massachusetts Lowell, Lowell, MA
1999-	Graduate Faculty, University of Massachusetts Amherst, Amherst, MA

Publications:

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02-07-08P03:14 RCVD

February 6, 2008

Robert L. Martin
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
U.S.A.

Re: Revised GRAS Notice for D-Ribose for Use as a Food Ingredient

Dear Dr. Martin:

As per the recommendations provided by the agency in response to our submission of the GRAS Exemption Claim on January 16, 2008, please accept the enclosed revised notice of a generally recognized as safe (GRAS) exemption claim for the use of D-ribose as a food ingredient, in compliance with the GRAS notification procedure described in Federal Register 62 FR 18937, dated April 17, 1997. Enclosed please find three (3) copies of the GRAS Notice, each containing: a signed exemption claim, detailed information on the notified substance, information on any self-limiting levels of use, and a detailed summary of the basis for the GRAS determination.

This notice replaces the original notice submitted on January 16, 2008.

I trust that you will find the enclosed notice acceptable. Please contact me *via* telephone [(763) 757-0032] or e-mail (BFaulken@bioenergy.com) should you have any questions regarding the submitted notice. I look forward to receiving acknowledgement of receipt of this notice.

Sincerely,

Bruce Faulken

Encl.

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

D-Ribose as defined in the report in Appendix I entitled, " **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE"**, dated November 29, 2007, has been determined by Bioenergy, Inc. to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, and on the consensus opinion of an independent panel of experts qualified by scientific training and expertise to evaluate the safety of D-ribose under the conditions of its intended use in food. Therefore, the use of D-ribose in food as described below is exempt from the requirement of premarket approval.

Signed,

2-6-08

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

Date

B. Name and Address of Notifier

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

C. Common Name of the Notified Substance

D-ribose

D. Conditions of Intended Use in Food

Bioenergy, Inc. intends to market D-ribose as an ingredient in beverages and beverage bases (calorie-reduced non-cola carbonated beverages, non-cola carbonated beverages, non milk-based meal replacements, sports, isotonic, and energy drinks), coffee and tea (instant tea, specialty and spiced teas), frozen dairy desserts and mixes (frozen yogurt, ice cream and frozen

milk desserts (excluding novelties)), grain products and pasta (energy and meal replacement bars), hard candy (selected hard candy), milk products (milk-based meal replacements, milk drinks (no malts or shakes), yogurts), processed fruits and fruit juices (calorie-reduced fruit drinks and ades, fruit juices, fruit nectars), processed vegetables and vegetable juices (vegetable juice) and soft candy (selected soft candy (excluding chocolate bars)) [see Appendix I - **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

The consumption of D-ribose from all proposed food uses was estimated using the proposed food uses and use levels in conjunction with food consumption data included in the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2007).

Approximately 83.4% of the total U.S. population was identified as consumers of D-ribose from the proposed food-uses (6,893 actual users identified). On an all-user basis, the mean intake of D-ribose by the total U.S. population from all proposed food-uses was estimated to be 3.39 g/person/day or 68.01 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of D-ribose the total U.S. population from all proposed food-uses was estimated to be 7.24 g/person/day or 153.45 mg/kg body weight/day.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, D-ribose has been determined by Bioenergy, Inc. to be GRAS on the basis of scientific procedures (U.S. FDA, 2007a). This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of D-ribose as a component of food. The safety of the ingredient is based on the results of published toxicological and clinical studies in animals and humans on D-ribose. The GRAS status of D-ribose is based on this available published scientific information in relation to the intended conditions of use of the ingredient in foods. [See Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Mr. Bruce Faulken
Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, Minnesota
55304

Should the FDA have any questions or additional information requests regarding this notification, Bioenergy, Inc. will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

D-Ribose is a white to slightly yellow crystalline powder, characterized by a fruity sweet odor and slightly sweet taste. It is chemically related to other 5-carbon monosaccharides, such as arabinose and xylose.

Common or Usual Name: D-ribose

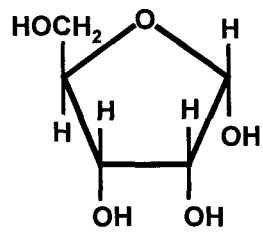
Chemical Name: A-D(-) ribofuranose

Chemical Abstracts Service (CAS) Number: 50-69-1

Empirical Formula: $C_5H_{10}O_5$

Molecular weight: 150.13

Structural Formula:



B. Method of Manufacture

D-ribose is produced by a non-genetically modified and non-sporulating strain of the microorganism *Bacillus subtilis* (*B. subtilis*), which accumulates D-ribose due to low transketolase activity, resulting in the inability of the organism to utilize this sugar. Transketolase is an enzyme that catalyzes the transfer of a 2-carbon fragment from xylulose 5-phosphate to ribose 5-phosphate, producing glyceraldehyde 3-phosphate and sedoheptulose 7-phosphate. The disruption in the metabolic pathway for D-ribose results in its accumulation.

In the U.S., carbohydrase (21 CFR §184.1148 [U.S. FDA, 2007b]) and protease (21 CFR §184.1150 [U.S. FDA, 2007c]) from *B. subtilis*, meeting food-grade specifications, are affirmed as GRAS for use in foods as enzymes at levels not exceeding current good manufacturing practice (cGMP) (U.S. FDA, 2007b,c). The affirmations are predicated on the use of nonpathogenic and nontoxigenic strains of *B. subtilis* (U.S. FDA, 2007b,c).

B. subtilis has traditionally been used in the commercial production of the Japanese delicacy natto by fermentation of soybeans, as well as in the commercial production of other compounds utilized in the food industry. Furthermore, *B. subtilis* is widely distributed in the environment and is naturally present in many foods that have been consumed by humans for decades with no evidence of food poisoning (Hui *et al.*, 2004; Logan *et al.*, 2007).

Following a careful review of the scientific and medical literature, Professor Eric Johnson (Food Research Institute, University of Wisconsin-Madison) concluded that *B. subtilis* is non-toxigenic and non-pathogenic. He also noted that antibiotic resistance would not be expected as there are no known plasmids in *B. subtilis* that encode for antibiotic resistance, and because D-ribose-producing strains of *B. subtilis* were developed through a process that does not lead to antibiotic resistance (UV mutagenesis).

The production of D-ribose is initiated by cultivating *B. subtilis* in a nutrient-rich medium, followed by fermentation. During fermentation, glucose is converted to D-ribose, which accumulates in the culture broth. The culture broth is filtered to remove bacterial cells and undergoes extensive purification, followed by concentration through evaporation and crystallization with ethanol. The crystals are recovered by centrifugation, then dried and packaged. The final product is of high purity (97 to 103% ribose).

C. Specifications for Food Grade Material

In order to ensure a consistent product, Bioenergy, Inc. established numerous specification parameters of the final ingredient (see Table 1), and representative lots of the manufactured product are routinely analyzed to verify that the manufacturing process produces a consistent product within final product physical, chemical, and microbiological parameters. D-ribose is produced in accordance with current Good Manufacturing Practices and meets appropriate food-grade specifications, and all raw materials and processing aids used in the manufacture of D-ribose, including water, activated carbon, sodium chloride, hydrochloric acid, ethanol, ion exchange resin, and defoaming agent, are permitted for use in food in the U.S. Furthermore, comprehensive analyses of potential residues from the manufacturing process have confirmed the purity of the final product (97 to 103% pure). For example, analytical procedures failed to detect the presence of yeasts, moulds, *Salmonella,* or *Escherichia coli.* Moreover, no proteins were detected in samples of 20% D-ribose solution as measured by the Bradford assay. Ethanol, as along with sugars and sugar alcohols produced in the fermentation process also are largely removed during purification.

Table 1 Chemical and Physical Specifications for D-Ribose

Specification Parameter	Specification	Method of Analysis
Appearance	Dry shape-holding characteristics with powdery texture that is white to slightly yellow in color.	Internal method (SOP-QC002-00)
Melting point	80 to 90°C	Internal method (derived from method I, CP2005 Appendix VI C)
Specific rotation	-19.0 to -21.0°	CP2005 Appendix VI E
D-ribose (purity)	97.0-103.0%	Internal method (SOP-QC002-00)
Loss on drying (moisture)	<2.0%	Internal method (derived from method I, CP2005 Appendix VIII L)
Ash	≤0.2%	CP2005 Appendix VIII N
Clarity of solution	≥95% transmittance	Bioenergy 30-014
Lead	≤0.1 ppm	AOAC 993.14
Arsenic	≤1 ppm	Method I, CP2005 Appendix VIII J
Total plate count	NMT 100 CFU/g	AOAC 990.12
Salmonella sp.	Negative/25g	AOAC 991.14
Coliforms	NMT 10 CFU/g	AOAC 992.21
Yeast and mold	NMT100 CFU/g	AOAC 992.11

Abbreviations: CFU, colony forming unit; NMT, not more than

III. Self-Limiting Levels of Use

There are no self-limiting technical attributes of D-ribose that would limit its use.

IV. Basis for GRAS Determination

The determination by Bioenergy, Inc. that D-ribose is GRAS is on the basis of scientific procedures [See Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**], which is supported by the views of experts, qualified by scientific training and experience to evaluate the safety of D-ribose under the intended conditions of use in food, as specified herein. The safe use of D-ribose is based on generally available published scientific information in relation to the intended conditions of use of the ingredient in foods. A summary of this information is provided in Appendix I [**EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE**].

V. References

CDC. 2006. Analytical and Reporting Guidelines: The National Health and Nutrition Examination Survey (NHANES). Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS); Hyattsville, Maryland. Available from: http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/nhanes_analytic_guidelines_dec_2005.pdf.

Hui, Y.H.; Meunier-Goddik, L.; Hansen, Å.S.; Josephsen, J.; Nip, W.-K.; Stanfield, P.S.; Toldrá, F. (Eds.). 2004. Handbook of Food and Beverage Fermentation Technology. Marcel-Dekker, Inc.; New York [919p].

Logan, N.A.; Popvic, T.; Hoffmaster, A. 2007. *Bacillus* and other aerobic endospore-forming bacteria. In: Murray, P.R.; Baron, E.J.; Jorgensen, J.H.; Landry, M.L.; Pfaller, M.A. (Eds.). Manual of Clinical Microbiology (9th Ed.). ASM Press; Washington, DC, Vol. 1, pp. 455-473.

U.S. FDA. 2007a. Part 170—Food labeling. Section § 170.30— Eligibility for classification as generally recognized as safe (GRAS). In: U.S. Code of Federal Regulations (CFR). Title 21: Food and Drugs (U.S. Food and Drug Administration). U.S. Food and Drug Administration (U.S. FDA). U.S. Government Printing Office (GPO); Washington, DC, pp. 13-15. Available from: http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr170.30.pdf.

U.S. FDA. 2007. Part 184—Direct food substances affirmed as generally recognized as safe. Section §184.1148—Bacterially-derived carbohydrase enzyme preparation. In: U.S. Code of Federal Regulations (CFR). Title 21: Food and Drugs (U.S. Food and Drug Administration). U.S. Food and Drug Administration (U.S. FDA). U.S. Government Printing Office (GPO); Washington, DC, pp. 500-501. Available from: http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr184.1148.pdf.

U.S. FDA. 2007. Part 184—Direct food substances affirmed as generally recognized as safe. Section §184.1150—Bacterially-derived protease enzyme preparation. In: U.S. Code of Federal Regulations (CFR). Title 21: Food and Drugs (U.S. Food and Drug Administration). U.S. Food and Drug Administration (U.S. FDA). U.S. Government Printing Office (GPO); Washington, DC, p. 501. Available from: http://a257.g.akamaitech.net/7/257/2422/26mar20071500/edocket.access.gpo.gov/cfr_2007/aprqtr/pdf/21cfr184.1150.pdf.

USDA. 2007. What We Eat in America: National Health and Nutrition Examination Survey (NHANES): 2003-2004. U.S. Department of Agriculture (USDA); Riverdale, Maryland. Available from: http://www.ars.usda.gov/Services/docs.htm?docid=13793#release.

SUBMISSION END

Bioenergy, Inc.
13840 Johnson St. NE
Ham Lake, MN 55304, USA
Phone 763.757.0032
Fax 763.757.0588
Web site www.bioenergy.com

March 27, 2008

Laura A. Dye
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
U.S.A.

Re: Additional Information and Corrections to GRAS Notice for D-Ribose for Use as a Food Ingredient (GRN 000243)

Dear Dr. Dye:

As per the recommendations provided by the agency during our teleconference on March 20, 2008, please accept the enclosed supplemental information and corrections to the generally recognized as safe (GRAS) exemption claim for the use of D-ribose as a food ingredient (GRN 000243). Please note the following changes to the GRAS Notice:

Section B. Method of Manufacture

1. Information regarding the strain of *Bacillus subtilis* (*B. subtilis*) used in the production of D-ribose (page 3) should be supplemented with the following information:

    a. Bioenergy employs *B. subtilis* American Type Culture Collection (ATCC) number 21951 for the production of D-ribose. This strain was developed through UV irradiation (254 nm).

    b. Methods of manufacture and strain development for D-ribose using *B. subtilis* strains similar to that used by Bioenergy have been patented. References for these patents are provided below.

Kishimoto, K.; Kintaka, K.; Uchiyama, N. (Inventors). 1990. Production of D-ribose. Assignee: Takeda Chemical Industries Ltd., Osaka Japan. U.S. Patent & Trademark Office; Washington, DC. United States Patent No. 4,904,587 (Feb. 27, 1990).

Sasajima, K.-I; Yoneda, M. (Inventors). 1975. Method of producing D-ribose. Assignee: Takeda Chemical Industries, Ltd., Osaka Japan. U.S. Patent & Trademark Office; Washington, DC. United States Patent No. 3,919,046 (Nov. 11, 1975).

Sasajima, K.-I.; Doi, M.; Fukuhara, T.; Yokota, A.; Nakao, Y.; Yoneda, M. (Inventors). 1976. Method for the production of D-ribose. Assignee: Takeda Chemical Industries Ltd., Osaka Japan. U.S. Patent & Trademark Office; Washington, DC. United States Patent No. 3,970,522 (July 20, 1976).

2. The first sentence of Section B (page 3) should be replaced with the following sentence: "D-ribose is produced by a non-sporulating strain of the microorganism *Bacillus subtilis* (*B. subtilis*), which accumulates D-ribose due to low transketolase activity, resulting in the inability of the organism to utilize this sugar." It should be noted that although the bacterial strain used in the production of D-ribose is genetically modified, it was not modified through recombinant technology.

3. The description of the manufacturing process (page 4) should be supplemented with the enclosed information that describes the current manufacturing process for D-ribose ("Manufacturing Process and Controls"). Please note that the current manufacturing process and the materials used in the process are slightly different from those described in GRN 000100 (original GRAS Notice for D-ribose).

Section C. Specifications and Lot Analyses for Food Grade Material

1. The ion exchange resin used in the manufacturing process consists of hydrolyzed polymers of methyl acrylate and divinylbenzene, and is permitted for use in the U.S. in the treatment of food (21 CFR 173.25).

2. The defoaming agent used in the manufacturing process is polypropylene glycol, which is permitted for use in the U.S. as a defoaming agent for beet sugar and yeast (21 CFR 173.340).

3. Table 1 (page 5) should be replaced with the enclosed revised Table 2.

4. The internal method for D-ribose purity in Table 2 (originally Table 1) is a high performance liquid chromatography (HPLC) method and is attached for your reference.

5. An additional table (Table 3, enclosed) providing data from analyses of 5 non-consecutive lots of D-ribose should be added following Table 1 (page 6).

6. The fermentation conditions are controlled to ensure that the only microorganisms present during fermentation are *B. subtilis* ATCC 21951. Air sparge rate and agitation is controlled in the fermentation. The conversion of glucose in the fermentation broth to D-ribose confirms that fermentation has been successful and no competing organisms are present. To verify the absence of the production organism or other contaminants in the final product, D-ribose is tested for total aerobic plate count, *Salmonella, sp.*, coliforms and yeast and mold. The final product is often tested for the presence of protein, endotoxins and antibiotic activity.

Section IV. Basis for GRAS Determination

1. In the reference list for Appendix I (EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS FOR THE PROPOSED FOOD USES OF D-RIBOSE), the references for Griffiths *et al.*, 2006a and Griffiths *et al.*, 2006b should be replaced with the following references:

Griffiths, J.C.; Borzelleca, J.F.; St. Cyr, J. 2007a. Sub-chronic (13-week) oral toxicity study with D-ribose in Wistar rats. Food Chem Toxicol 45(1):144-152.

Griffiths, J.C.; Borzelleca, J.F.; St. Cyr, J. 2007b. Lack of oral embryotoxicity/teratogenicity with D-ribose in Wistar rats. Food Chem Toxicol 45(3):388-395.

I trust that you will find the enclosed information acceptable. Please contact me *via* telephone [(763) 757-0032] or e-mail (BFaulken@bioenergy.com) should you have any questions.

Sincerely,

(b)(6)

Bruce Faulken

Encl.

Replacement Pages for GRAS Notice 000243 (D-ribose)

Manufacturing Process and Controls (to supplement Section B)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

From: Bruce Faulken [BFaulken@bioenergy.com]
Sent: Monday, July 21, 2008 10:02 AM
To: Dye, Laura
Subject: RE: FDA Questions About GRN 243, D-ribose

Ms. Dye: Our response has taken longer than I'd like but we want to be thorough. And, we utilize some resources outside the company. With vacations, there has been some delay. I do hope to have our response to you this week. It is in its final draft.

Bruce Faulken

From: Dye, Laura [mailto:Laura.Dye@fda.hhs.gov]
Sent: Monday, July 21, 2008 5:42 AM
To: Bruce Faulken
Subject: RE: FDA Questions About GRN 243, D-ribose

Good Morning Mr. Faulken,

How does it look to receive your amendment? Would it be this week?

Many thanks,

Laura Dye

Ms. Laura A. Dye, Consumer Safety Officer
Food and Drug Administration
Office of Food Additive Safety
Division of Petition Review
Mailing Address:
5100 Paint Branch Parkway, HFS-265
College Park, MD 20740
Phone: 301-436-1275
FAX: 301-436-2972
e-mail: Laura.Dye@fda.hhs.gov

From: Bruce Faulken [mailto:BFaulken@bioenergy.com]
Sent: Tuesday, July 01, 2008 1:02 PM
To: Dye, Laura
Subject: RE: FDA Questions About GRN 243, D-ribose

Dear Ms. Dye: Unfortunately, vacations have intervened and we have not completed our response. We are trying to be thorough. It looks like it will not be ready now until next week.

Bruce Faulken

From: Dye, Laura [mailto:Laura.Dye@fda.hhs.gov]
Sent: Tuesday, July 01, 2008 10:12 AM
To: Bruce Faulken
Subject: RE: FDA Questions About GRN 243, D-ribose

Good Morning Mr. Faulken,

How are we doing? Does it look like we will receive your package soon?

Very best regards,

Laura Dye

Ms. Laura A. Dye, Consumer Safety Officer
Food and Drug Administration
Office of Food Additive Safety
Division of Petition Review
Mailing Address:
5100 Paint Branch Parkway, HFS-265
College Park, MD 20740
Phone: 301-436-1275
FAX: 301-436-2972
e-mail: Laura.Dye@fda.hhs.gov

From: Bruce Faulken [mailto:BFaulken@bioenergy.com]
Sent: Thursday, June 19, 2008 10:41 AM
To: Dye, Laura
Subject: RE: FDA Questions About GRN 243, D-ribose

Dear Ms. Dye:

Thank you for your e-mail. Our team is working on the response and, hopefully, will get back to you next week.

Bruce Faulken
General Counsel

From: Dye, Laura [mailto:Laura.Dye@fda.hhs.gov]
Sent: Wednesday, June 18, 2008 1:39 PM
To: Bruce Faulken

Subject: FDA Questions About GRN 243, D-ribose
Importance: High

Dear Mr. Faulken:

Our FDA GRAS review team has a few questions about your notice, GRN 243, D-ribose, requiring clarification and/or comment.

Microbiology

In the amendment dated March 27, 2008, Bioenergy provided clarifying information regarding the strain and method of manufacture, noting that *Bacillus subtilis* ATCC 21951 is used as the production organism and citing several patents as similar in strains and process to that used by Bioenergy in its production of ribose.

1. One can infer from the manufacturing information in that amendment that the strain is grown in a fermentation broth with glucose as the carbon source and added aromatic amino acids and that said medium is aerated. Is this inference correct?

2. The notice and amendment refer to the strain as having "low transketalase activity, resulting in the inability of the organism to utilize this sugar." A publication by De Wulff et al. (Journal of Applied Microbiology, 1997 83:25-30) describes this activity as being reduced, but not particularly low (60 percent of wild-type), which would result in a reduction rather than an inability of utilization of ribose by the production microorganism. Do we understand this correctly?

3. The GRAS Panel report states: It is unlikely that the microorganism (*B. subtilis*) would be present in the final product given the purification process. This is supported through the high level of purity of the final product (97 to 103% ribose) and the fact that analytical procedures failed to detect the presence of yeasts, moulds, Salmonella, or Escherichia coli. Furthermore, no proteins were detected in samples of 20% D-ribose solution as measured by the Bradford assay."

We're not sure that we understand the thinking here - the yeast, "mould," Salmonella, and E. coli levels are not relevant to residual *B. subtilis,* and the sensitivity of the protein assay would be unlikely to be sensitive enough to detect very small numbers of cells. The aerobic plate counts does allow for no more than 100 CFU/g. Moreover, the procedures are such that it would be extremely unlikely for vegetative cells of *B. subtilis* to remain with the crystallized ribose. I think you could say that the purity, manufacturing process and total aerobic counts support that the production microorganism is not likely to be present in the final product. However, the specifications do not in themselves verify the absence of the production microorganism, and commonly, the production microorganism is itself a microbiological specification that is not detectable at some level. Please comment/clarify.

Chemistry

In the amendment, Bioenergy also stated that the HPLC method was enclosed for our review. Unfortunately, the mailing we received did not contain this information. In addition, what is the associated temperature for the specific rotation specification? Using your specific method of manufacture are there any byproducts formed?

Toxicology

Bioenergy describes its methods of manufacture for D-ribose using *B. subtilis* as “similar to” other patented production methods [US Patent 4,904,587 (Kishimoto *et al.,* 1990); US Patent 3,919,046 (Sasajima and Yoneda, 1975); and US Patent 3,970,522 (Sasajima *et al.,* 1976)]. Regarding your specific method, are there metabolites/byproducts formed? If so, what is the toxicological profile of each?

Intended Use

What is the intended use of D-ribose? For example, is it to impart sweetness, provide bulk, or another use in the food product? Your notice did not explicitly provide your intended use for D-ribose. Lastly, how did you determine specific intended use, was intake estimated on chronic per day or per eating occasion?

If you should have any questions or comments about our request for additional information, you may contact me at my email address or by telephone as indicated below. Thank you in advance for responding to this email with an express mailing/electronic submission of the aforementioned information as soon as possible please.

Sincerely,

Laura Dye
Ms. Laura A. Dye, Consumer Safety Officer
Food and Drug Administration
Office of Food Additive Safety
Division of Petition Review
Mailing Address:
5100 Paint Branch Parkway, HFS-265
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Phone: 301-436-1275
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July 30, 2008

Ms. Laura A. Dye
Food and Drug Administration
Office of Food Additive Safety

5100 Paint Branch Parkway, HFS-265
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Phone: 301-436-1275
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Re: Responses to Questions from FDA Regarding GRAS Notice for D-Ribose for Use as a Food Ingredient (GRN 000243)

Dear Ms. Dye,

Please find below our responses to questions regarding the Generally Recognized as Safe (GRAS) Notice for D-ribose (GRN 000243), received on June 18, 2008. The text of each question or comment is included for your convenience.

Microbiology

In the amendment dated March 27, 2008, Bioenergy provided clarifying information regarding the strain and method of manufacture, noting that Bacillus subtilis ATCC 21951 is used as the production organism and citing several patents as similar in strains and process to that used by Bioenergy in its production of ribose.

1. *One can infer from the manufacturing information in that amendment that the strain is grown in a fermentation broth with glucose as the carbon source and added aromatic amino acids and that said medium is aerated. Is this inference correct?*

   Response: Yes, this is correct.

2. *The notice and amendment refer to the strain as having "low transketalase activity, resulting in the inability of the organism to utilize this sugar." A publication by De Wulff et al. (Journal of Applied Microbiology, 1997 83:25-30) describes this activity as being reduced, but not particularly low (60 percent of wild-type), which would result in a reduction rather than an inability of utilization of ribose by the production microorganism. Do we understand this correctly?*

   Response: Yes, but it is our belief that the transketolase activity is less than 60% of wild type strains. This belief is supported by the observation that current fermentation yields are greater than those yields of fermentations early on in the

development process, and as compared to those yields of other ribose-producing strains.

3. *The GRAS Panel report states: It is unlikely that the microorganism (B. subtilis) would be present in the final product given the purification process. This is supported through the high level of purity of the final product (97 to 103% ribose) and the fact that analytical procedures failed to detect the presence of yeasts, moulds, Salmonella, or Escherichia coli. Furthermore, no proteins were detected in samples of 20% D-ribose solution as measured by the Bradford assay."*

   We're not sure that we understand the thinking here - the yeast, "mould," Salmonella, and E. coli levels are not relevant to residual B. subtilis, and the sensitivity of the protein assay would be unlikely to be sensitive enough to detect very small numbers of cells. The aerobic plate counts does allow for no more than 100 CFU/g. Moreover, the procedures are such that it would be extremely unlikely for vegetative cells of B. subtilis to remain with the crystallized ribose. I think you could say that the purity, manufacturing process and total aerobic counts support that the production microorganism is not likely to be present in the final product. However, the specifications do not in themselves verify the absence of the production microorganism, and commonly, the production microorganism is itself a microbiological specification that is not detectable at some level. Please comment/clarify.

   Response: The extensive purification steps undertaken in the manufacturing process, including a series of filtration steps to remove bacteria and bacterial fragments from the culture broth, evaporation, and crystallization with ethanol, and drying at high temperature, ensure that the production organism will not be present in the final product. Therefore, we believe it is not necessary to add limits for *B. subtilis* to the product specifications.

Chemistry

In the amendment, Bioenergy also stated that the HPLC method was enclosed for our review. Unfortunately, the mailing we received did not contain this information. In addition, what is the associated temperature for the specific rotation specification? Using your specific method of manufacture are there any byproducts formed?

Response: The HPLC method is attached with our apologies for the previous omission. The associated temperature for the specific rotation specification is: -19.0 °C to -21.0°C. No byproducts have been detected above the limit of detection at a level of 0.5% (please see the response to the Toxicology question below).

Toxicology

Bioenergy describes its methods of manufacture for D-ribose using B. subtilis as "similar to" other patented production methods [US Patent 4,904,587 (Kishimoto et al., 1990); US Patent 3,919,046 (Sasajima and Yoneda, 1975); and US Patent 3,970,522 (Sasajima et al., 1976)]. Regarding your specific method, are there metabolites/byproducts formed? If so, what is the toxicological profile of each?

Response: Using Bioenergy's specific methods of analysis no metabolites or by products were detected above the limit of detection at a level of 0.5%. All components of the final product occurring at levels of 0.5% or greater have been identified and are presented in the product specifications.

Furthermore, the lack of toxicological concerns related to the "potential formation" of metabolites or by products has been confirmed through the lack of any significant adverse effects reported in pre-clinical (90-day study) and human studies conducted on D-ribose produced from *B. subtilis*, Moreover, *B. subtilis* is considered to be non-pathogenic and non-toxigenic and has a safe history of use in the production of enzymes for use in foods, as well as in the production of traditional foods (*e.g.*, natto). Therefore, all components of the final product are considered safe under the intended conditions of use.

Intended Use

What is the intended use of D-ribose? For example, is it to impart sweetness, provide bulk, or another use in the food product? Your notice did not explicitly provide your intended use for D-ribose. Lastly, how did you determine specific intended use, was intake estimated on chronic per day or per eating occasion?

Response: D-Ribose is intended for use as a nutritive ingredient.

With respect to our selection of foods to include, we looked at uses that we thought were commercially viable. We have had discussions over a number of years with manufacturers of various products and have a good idea of what areas to focus on.

Estimates for the daily intake of D-ribose from the consumption of proposed food uses represent projected 2-day averages using NHANES 2003-2004 data. Thus, estimates do not reflect either acute (per eating occasion) or chronic intakes; however, the 2-day data are used as an estimate of chronic intakes.

Please contact me via telephone [(763) 757-0032] or e-mail (BFaulken@bioenergy.com) should you have any questions.

Sincerely,

(b)(6)

Bruce Faulken

Encl.

(b)(4)

(b)(4)

BIOENERGY INC.

August 15, 2008

Ms. Laura A. Dye
Food and Drug Administration
Office of Food Additive Safety

5100 Paint Branch Parkway, HFS-265
College Park, MD 20740
Phone: 301-436-1275
FAX: 301-436-2972
e-mail: Laura.Dye@fda.hhs.gov

Re: Responses to Questions from FDA Regarding GRAS Notice for D-Ribose for Use as a Food Ingredient (GRN 000243)

Dear Ms. Dye,

Please find below our responses to questions regarding the Generally Recognized as Safe (GRAS) Notice for D-ribose (GRN 000243), received on August 12, 2008 and discussed in our teleconference on August 14, 2008. The text of each question or comment is included for your convenience.

1. *On page (p.) 23, Bioenergy states that "D-ribose would be included as an ingredient in food and beverage products with additional sources of energy in the form of carbohydrate that would likely provide sufficient amounts of glucose to ameliorate the blood glucose lowering effects of D-ribose." Reduced-calorie beverages are listed among the intended uses in Table 2 (p. 23) of the GRN. Low-calorie beverages are not listed. However, Bioenergy states on p. 12 that "although low-calorie beverages will not provide additional sources of energy, these beverages will contain less than 3 g D-ribose."*

   Do the intended uses in GRN 243 include low-calorie beverages or only reduced-calorie beverages?

   If low-calorie beverages are included in the intended use, please provide a further discussion of the general recognition of safety of ribose use in low-calorie beverages at a level of 0.4% (providing approximately 2.8 g/bottle). In this discussion, please address any conditions of safe use for the population in general and for diabetics.

   Response: D-Ribose is intended for use in reduced-calorie beverages but not in low-calorie beverages. In the Notice and accompanying Expert Panel Consensus Statement, any reference to "low-calorie beverages" should be replaced with "reduced-calorie beverages."

2. *In Bioenergy's amendment, you indicate that "The associated temperature for the specific rotation specification is: -19.0 (degrees) C to -21.0 (degrees) C." However, in the notice -19 to -21 degrees is given as the specification for optical rotation.*

Degrees of optical rotation are not equivalent to degrees Celsius. Generally, the conditions of measurement (e.g. temperature, concentration of solution) of optical rotation are specified. For example, Dean's Analytical Chemistry Handbook (2nd edition) gives the specific rotation for ribose as -25 degrees at a concentration of 4 g/100 mL in water and temperature of 24 degrees Celsius.

Please provide a reference to method or relevant details associated with this specification.

Response: Information regarding the specific rotation test procedure is as follows:

The specific rotation is calculated from observed optical rotation in the test solution obtained as directed herein. Measurements are made with a photoelectric polarimeter or visual polarimeter at 589 nm (D line of sodium). When a photoelectric polarimeter is used, a single measurement, corrected for the solvent blank, is made. When a visual polarimeter is employed, the average of no fewer than five determinations, corrected for the reading of the same tube with a solvent blank, is used.

Prepare a solution containing 4-g of a previously dried sample in a sufficient volume of water to make 100-ml total volume (4% w/v). The optical rotation is determined at a temperature of 20±0.5°C.

Calculate the specific rotation with reference to the anhydrous substance using the formula:

$$[\alpha]_D^{20oC} = \alpha \text{ X } 100/L \text{ X } C$$

Where,

D = D line of sodium;
α = the corrected observed rotation in degrees;
L = length of the polarimeter tube in decimeters (dm);
C = concentration (g) of the test substance in 100-ml of solution.

The specific optical rotation should be -19° to -21°.

Please contact me via telephone [(763) 757-0032] or e-mail (BFaulken@bioenergy.com) should you have any questions.

Sincerely,

(b)(6)

Bruce Faulken

Encl.

BIOENERGY INC.

September 30, 2008

Ms. Laura A. Dye
Food and Drug Administration
Office of Food Additive Safety
5100 Paint Branch Parkway, HFS-265
College Park, MD 20740

By e-mail

Re: Responses to Questions from FDA Regarding GRAS Notice for D-Ribose for Use as a Food Ingredient (GRN 000243)

Dear Ms. Dye:

The following are the responses of Bioenergy, Inc. to the questions raised in your e-mail of today's date:

We can confirm that the first four studies cited in your e-mail are unpublished but not confidential.

We also confirm that the latter two studies cited in your e-mail are not confidential and are publicly available.

Lastly, we confirm that the words "excluding confidential information" may be stricken from the cited sentence on page 1. Therefore, the information reviewed by the GRAS Panel is publicly available.

Sincerely,

(b)(6)

Bruce C. Faulken
General Counsel

cc: Ashley Roberts
Andrea Wong

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