DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date NOV 17 1997

From Acting Director, Division of Programs & Enforcement Policy, Office of Special Nutritionals, HFS-455

Subject 75-day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Alpha-D(-)ribofuranose
Firm:	Humanetics Corp. 600 South Highway 169 Suite 1205 St. Louis Park, MN 55426
Date Received by FDA:	October 28, 1997
90-Day Date:	January 27, 1998

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after January 20, 1998.

James T. Tanner, Ph.D.

Attachment

cc:
HFS-22 (CCO)
HFS-450 (w/cpy incoming, OSN#55437, r/f)
HFS-456 (File)
f/t:HFS-456:rjm:11/12/97:DocName:55437.MEM:disc24

95S-0316

RPT 21

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

NOV 17 1997

Mr. Ronald J. Zenk
President and CEO
Humanetics Corporation
600 South Highway 169
Suite 1205
St. Louis Park, Minnesota 55426

Dear Mr. Zenk:

This is in response to your letter of October 21, 1997 to the Food and Drug Administration (FDA) pursuant to section 413 of the Federal Food, Drug, and Cosmetic Act (the act) concerning the marketing of alpha-D(-)ribofuranose as a new dietary ingredient.

Section 413 of the act requires a manufacturer or distributor of a dietary supplement which contains a new dietary ingredient to submit certain information to the agency. Specifically, the act requires that at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient provide the FDA with information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe. Because you submitted to FDA information which is the basis on which you concluded that the dietary supplement will reasonably be expected to be safe, the agency will consider your submission to be the required 75-day premarket notification of your intent to sell alpha-D(-)ribofuranose as a dietary supplement. As required by section 413(a)(2) of the act, we will keep your submission confidential for 90 days from the date of receipt, and on January 20, 1998, it will be placed on public display at Dockets Management Branch. Commercial and confidential information in the notification will not be made available to the public.

Be advised that there is no requirement that dietary supplements be approved by the FDA prior to marketing. It is the responsibility of the person who introduces a dietary supplement into interstate commerce to ensure that the dietary supplement is safe for its intended use and is properly labeled.

Please contact us if we may be of further assistance.

Sincerely,

James T. Tanner, Ph.D.
Acting Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

cc:
HFA-224 (w/incoming)
HFA-305 (docket 97S-0316)
HFS-22 (CCO)
HFS-456 (File)
HFS-450 (file, r/f)
f/t:HFS-456:rjm:11/12/97:docname:55437.adv:disc24

HUMANETICS
CORPORATION

October 21, 1997

Linda S. Kahl, Ph.D.
Office of Special Nutritionals
Center for Food and Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW (HFS-450)
Washington, DC 20204

Dear Dr. Kahl:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, Humanetics Corporation, on its own behalf and on behalf of Bioenergy, Inc., Minneapolis, Minnesota, wishes to notify the Food and Drug Administration that it will market a new dietary ingredient, alpha-D(-) Ribofuranose (Ribose), a naturally-occurring simple sugar found in all foods. Accordingly, enclosed are two (2) copies of this notification.

The dietary supplement that contains Ribose will consist of up to five (5) grams of Ribose in liquid or capsule form for ingestion which will be suggested to be taken two to four times per day.

Attached is a summary and reports of the safety studies and other information which establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. These supporting studies include:

(1) A seven page safety profile summary of Ribose with reference to two exhibit tables and published literature.

(2) Ten preclinical pharmacology and toxicology reference reprints on Ribose.

(3) Fifteen clinical trial reference reprints on Ribose.

(4) Two general clinical review reprints on Ribose.

Sincerely,

Ronald J. Zenk
President & CEO

cc: Mr. Clarence Johnson
President
Bioenergy, Inc.

600 South Highway 169 • Suite 1205 • St. Louis Park, MN 55426 • (612) 513-9246 • (612) 513-9049 (fax)

Alpha-D(-)Ribofuranose (Ribose)

Basis for Concluding New Dietary Ingredient will Reasonably be Expected to be Safe

Background

Alpha-D(-)Ribofuranose (Ribose) is a naturally-occurring simple sugar found in all foods and tissues. It is currently approved for use as a food additive. Several clinical trials with Ribose have been performed with oral and intravenous administration routes. Oral doses in humans up to (*i*) 130 grams over a 10 hour period and (*ii*) 60 grams per day for seven days have been given. In these clinical trials, Ribose has been well-tolerated with the exception of an asymptomatic transient hypoglycemic effect noted. Preclinical animal studies further support the safety of Ribose. Ribose is used in the body as a precursor for ATP production, thus assisting cells in regenerating a natural energy supply.

Safety Assessments

Genotoxicity

In mutagenicity studies of non-irradiated and γ-irradiated, oxygenated and deoxygenated solutions of various monosaccharides, Wilmer et al.[1] reported on the mutagenicity of a 0.01 M solution of Ribose (in phosphate buffer) using the Salmonella typhimurium tester strains TA 100 and TA 98 in the plate-incorporation (Ames) assay and the preincubation (Yahagi) assay. Data indicates that Ribose did not cause a significant (eg. no effect to less than two-fold) increase in TA 100 or TA 98 revertants at any of the doses tested (0.15 to 1.2 grams/plate).

In Vitro Effects

At high concentrations, a number of monosaccharides, including Ribose, may partially inhibit lymphocyte proliferation in allogenic mixed lymphocyte cultures at a concentration of 50

mM. At such high levels, Ribose may also inhibit lectin (PHA)-induced proliferation. These results prompted Marini et al.[2] to study the effects of Ribose on the proliferation of other cell types *in vitro*. These investigators found that high concentrations of Ribose (25-50 mM; 3.75-7.50 mg/mL for 72 hours) that are several fold greater than those expected to be produced by the recommended dose herein, inhibited DNA, RNA and protein synthesis in a wide variety of cells (dividing and nondividing, normal and neoplastic, freely floating and substrate adhering) of human and mouse origin, at which levels other simple sugars have no such effect. In proliferating lymphocytes, Zunica et al.[3] speculate that Ribose may interfere with metabolic pathways critical for repair of DNA breaks since these cells must rejoin physiologically-formed DNA strand breaks in order to enter the cell cycle. These authors reported that some reducing sugars, such as D-glucose, at concentration of 25-50 mM are able to kill cells *in vitro* by damaging their DNA as evidence of unscheduled DNA synthesis (UDS). Given that these effects were seen *in vitro* in the absence of metabolic activities of blood and tissues, and that they occurred at high concentrations, there is likely no clinical significance to these findings.

Safety Studies in Animals

Marini et al.[2] reported that Ribose was devoid of *in vivo* toxicity when administered for several days to mice at concentrations known to inhibit cell proliferation *in vitro*.

Angello et al.[4] reported that samples from ischemic and normal regions of myocardium from young pigs (17 treated, nine in control group) exposed to Ribose solutions intravenously (3.3 mg/kg/min at 1.0 ml/min for 30 min) were normal as determined by triphenyl tetrazolium chloride (TTC) tissue staining. This dose (about 100 mg/kg) would be equivalent to a seven gram dose in a 70 kg person. These investigators reported that there were no significant differences between groups in heart rate, arterial blood pressure, mean serum glucose, mean

serum insulin or in regional myocardial blood flows. The mean decreases in serum glucose between pre-infusion and 60 minutes post-fusion were 13.8 and 0.0 mg/dL for the Ribose and saline groups, which was not a statistically significant difference. In a further study in the porcine model, the investigators also reported no clinically significant adverse experiences.[5]

In two studies in dogs, Foker demonstrated that intravenous infusions of Ribose for two days[6] or five days[7] at rates of 17 grams/day (550-700 mg/kg; equivalent to approximately 40-50 grams/day in humans) were well tolerated and no adverse experiences were noted.

Preclinical studies show that oral or intravenous administration of Ribose produces transient hypoglycemia accompanied by release of insulin in some animals. The effects of oral and intravenous administration of Ribose (50% solution, 3 ml/kg) on serum insulin levels was studied in male and female adult rabbits.[8] Intravenous injection of Ribose led to a moderate but significant ($p<0.05$) increase in serum insulin after injection compared to control animals that received normal saline only. The elevation in serum insulin level was sustained over a 120 minute period despite a decrease in blood Ribose levels over time. The data suggested that blood glucose was lower at five minutes postdose than at 0, 15, 30 or 60 minutes. The investigators reported that Ribose given orally, however, did not cause a significant (i.e., $p>0.05$) increase in serum insulin in this study. Blood glucose concentration also did not change significantly (i.e., $p>0.05$) following oral administration.

Administration of Ribose was reported to cause release of insulin in dogs; Halter et al.[9] administered Ribose intravenously (5% or 25% solutions at 0.76 ml/minute for 15 minutes) or by oral gavage (12 ml of 5% or 25% solutions) to fasted, mongrel dogs. These investigators concluded that intravenous administration of Ribose was more consistent in causing insulin release than Ribose given orally.

The effects of Ribose on blood glucose levels are not consistently seen in all species. Naito[10] reported that administration of Ribose to rabbits and mice caused a rise in blood glucose rather than a decrease as is observed in humans, dogs and rats. Also, elevation of serum insulin upon intravenous administration does not appear to be specific to Ribose. Intravenous doses of glucose, mannose and fructose (readily metabolized sugars) and glycine or oral doses of glucose, galactose and xylose cause serum insulin to increase in rabbits.[8] Ribose and other monosaccharides may indirectly stimulate insulin release in rabbits through some metabolite. For example, Nijjar[8] reported that intravenous injection of pyruvate enhanced the secretion of insulin in rabbits. There is some evidence that galactose and xylitol may also indirectly stimulate the release of insulin.[11] The effects of Ribose on blood glucose in humans is discussed in the following section.

Clinical Safety Studies

Ribose has been administered orally and intravenously in a wide range of doses to many patients and healthy volunteers. Studies have been carried out in healthy volunteers to evaluate the pharmacokinetics and metabolism of Ribose and the effect of Ribose on serum insulin and glucose. Studies have also been carried out in patients with coronary artery disease, angina, patients recovering from heart surgery, patients with myoadenylate deaminase deficiency and in diabetics. No serious adverse experiences clearly associated with Ribose were reported in these studies with the exception of an asymptomatic transient reduction in blood glucose.

The exhibits to this report summarize published clinical studies with intravenous Ribose (Exhibit A) and oral administration of Ribose (Exhibit B). In some studies, patients or subjects received more than one dose and some received oral and intravenous Ribose. The exhibits

assume that the mean weight was 70 kg when the dose is given as mg/kg without body weights. In the intravenous studies, the consensus safety assessment was that there were no clinically significant adverse effects of Ribose; mean serum glucose falls after Ribose administration but symptomatic hypoglycemia, however, did not occur. The results of the oral clinical trials can also be summarized regarding safety concerns: Ribose was very well tolerated at 60 grams per day for seven days in controlled trials and for two years in an uncontrolled case report study, and at an extremely high level of 130 grams given over a 10 hour period. Diarrhea was noted to occur at single oral doses greater than 10-20 grams.[12, 15, 24] Transient hypoglycemia occurs but it was not deemed to be clinically significant or symptomatic.

It has been well established that Ribose administration consistently reduces blood glucose in humans. Ginsberg et al.[15] gave 1 gm/kg oral or 15 grams intravenous (using a 7.5% solution over four minutes, 54 mg/kg/min.) Ribose to 10 normal subjects. Five received oral and five intravenous Ribose. Mean blood glucose decreases were 14 mg per 100 ml and 15 mg per 100 ml after the oral and intravenous administration of Ribose respectively. After intravenous administration of Ribose the nadir occurred at approximately one hour and blood sugar had returned to baseline within two hours after injection. Plasma insulin increased peaking rapidly, within minutes. There were no changes in blood cortisol or human growth hormone. The lowest recorded blood glucose after intravenous Ribose was 39 mg per 100 ml, occurring 30 minutes after Ribose, apparently asymptomatic. After oral Ribose there was a biphasic increase in insulin which was sustained and a biphasic decrease in blood glucose; the lowest measured was 45 mg per 100 ml, again asymptomatic. In this study the increase in serum insulin was more sustained than that reported by Steinberg (below) and recovery from hypoglycemia was associated with

return of plasma insulin to basal level. These authors concluded that insulin release induced by Ribose administration probably contributes to the decrease in blood sugar.

Additional published studies that evaluated oral Ribose include that of Steinberg et al.[26] who gave 15 grams of oral Ribose in six ounces of water over five minutes to 13 healthy volunteers and to 21 subjects with diabetes (six probable, five mild, five on oral hypoglycemic agents and five insulin-dependent). The lowest glucose levels occurred between 45 and 75 minutes postdose with the decreases in blood sugar being maximal in healthy volunteers and delayed as well as smaller in noninsulin-dependent diabetics. The insulin-dependent diabetics had a response that persisted for at least two hours. The serum insulin increase was however, larger in the diabetic patients than in healthy volunteers but these increases were transient and not statistically significant. There were substantial differences in insulin measurements in subjects in whom the test was performed twice.

In a study by Gross and Zollner,[25] eight subjects received 83.3 mg/kg/hr oral Ribose hourly for five hours and then 166.7 mg/kg/hr for an additional five hours. One subject received 130 grams of Ribose over this 10 hour period. Initial serum glucose averaged 73.5 mg/dl and was 68.4 and 55.8 mg/dl respectively for each dose level after five hours. Serum insulin (uU/mL) was 8.4 predose, 7.0 after the low dose and 10.4 after the high (166.7 mg/kg/hr) dose. The changes were asymptomatic in all cases. In this study average serum Ribose rose from baseline levels of 0.22 mg/mL to 3.20 mg/mL. However, Ribose is cleared rapidly ($t_{1/2}$ about 18-26 minutes) after administration[27] and thus poses no chronic accumulation safety-related issues. For example, in the study by Zollner et al[24], repeat oral doses of 1.12 grams of Ribose every five minutes for 260 minutes (about 60 grams total), produced a maximum serum Ribose concentration of 3.4 mM; this concentration had little or no effect in the *in vitro* experiments.[1,2,3]

In conclusion, studies in humans demonstrate that the only safety issue clearly related to administration of Ribose is decreased blood sugar. Published results suggest a possible dose-response with reduction in blood sugar generally of about 10-15% at doses of less than 10 grams. Doses greater than 10 grams produce larger, but more variable decreases. The hypoglycemic effect is however, transient and effects on glucose were clinically non-significant and asymptomatic.

Dose Considerations

Selection of the doses of Ribose for human consumption as a dietary supplement was determined from assessment of all the available animal and human clinical trial data using both oral and intravenous administration results to fully evaluate safe exposure levels. Doses of greater than 0.5 to about 1.0 gram/kg have been given to various animal species. Similarly, doses of 60 grams per day (about 1 gram/kg) have been given to humans in controlled trials for seven days. A case study presented earlier in this report indicated one individual has taken this level of Ribose for two years. In another clinical trial, a total oral dose of up to 130 grams of Ribose was given over 10 hours without clinical consequence.

It is therefore determined that a dose of up to five (5) grams (i.e. less than 0.1 gram/kg) taken two to four times daily would be well tolerated and elicit no chronic adverse health effects. This suggested dose level is well below that recommended by Zollner et al[24] whose many years of clinical experience with Ribose led them to conclude that, due only to the limitations based on *in vitro* data, the total oral daily dose in humans should not exceed one gram per kilogram of bodyweight per day (e.g., 70 grams per day for a 70 kilogram person), but that this dose level is well tolerated even over prolonged periods.

Exhibit A

Intravenous Ribose

Author	Number of Patients/ Subjects	Dose Range	Duration	Title of Study	Safety Results
Segal and Foley[12]	10	3-20g	105 min.	The Metabolism of D-Ribose in Man.	No complaints of hypoglycemic symptoms.
Goodman and Goetz[13]	10	35g	35 min.	Oral and Intravenous D-Ribose and Plasma Insulin in Healthy Humans: Effects of Route of Administration of Epinephrine and Propranolol.	Change in peripheral insulin levels after Ribose administration is modest.
Gross et al.[14]	5	26.7-71g	12 hrs.	Metabolism of D-Ribose Administered Continuously to Healthy Persons and to Patients with Myoadenylate Deaminase Deficiency.	Intravenous administration of up to 222 mg/kg/hr was well tolerated.
Ginsburg et al.[15]	5	15g	4 min.	Hormonal Changes During Ribose-induced Hypoglycemia.	No changes in blood pressure or pulse rate and no abdominal symptoms.
Steinberg et al.[16]	12	3.75-15g	Up to 20 min.	The Effect of D-Ribose Infusion on Serum Immuno-Reactive Insulin and Glucose Concentration.	Hypoglycemia observed may not relate to changes in insulin changes.
Bierman et al.[17]	8	40-50g	1 hr.	Metabolism of D-Ribose in Diabetes Mellitus.	Ribose can be utilized by the diabetic and did not contribute to hyperglycemia.
Hegewald et al.[18]	15	6.9g	30 min.	Ribose Infusion Accelerates Thallium Redistribution with Early Imaging Compared with Late 24-Hour Imaging without Ribose.	Changes in glucose and insulin levels were small compared to after eating.
Perlmutter et al.[19]	17	6.9g	30 min.	Ribose Facilitates Thallium-201 Redistribution in Patients with Coronary Artery Disease.	No patient developed symptomatic hypoglycemia or required treatment. No adverse reactions were noted.

Exhibit B

Oral Ribose

Author	Number of Patients/ Subjects	Dose Range	Duration	Title of Study	Safety Results
Goodman and Goetz[13]	10	35g	35 min.	Oral and Intravenous D-Ribose and Plasma Insulin in Healthy Humans: Effects of Route of Administration of Epinephrine and Propranolol.	No hypoglycemic symptoms reported.
Gross et al.[14]	13	26.7-48.7g	5 hrs.	Metabolism of D-Ribose Administered Continuously to Healthy Persons and to Patients with Myoadenylate Deaminase Deficiency.	Ribose was well tolerated. Doses over 200 mg/kg/ hr cause diarrhea.
Ginsburg et al.[15]	5	70g	Single dose	Hormonal Changes During Ribose-induced Hypoglycemia.	No changes in blood pressure or pulse rate. Diarrhea occurred in two subjects.
Wagner et al.[20]	3	>18g	>1 hr.	Effect of Oral Ribose on Muscle Metabolism During Bicycle Ergometer in AMPD-Deficient Patients.	Ribose may have therapeutic value in AMPD patients; apparently well tolerated.
Gross et al.[21]	10	12g	30 min.	Ribose Administration during Exercise: Effects of Substrates and Products of Energy Metabolism in Healthy Subjects and a Patient with Myoadenylate Deaminase Deficiency.	Difference in glucose decrease with and without Ribose was not significant during exercise.
Pliml et al.[22]	20	60g daily	3 days	Effects of Ribose Exercise-Induced Ischemia in Stable Coronary Artery Disease.	No changes in blood pressure, heart rate or rate-pressure product. Discussion mentions no lasting or damaging side effects of Ribose.
Steele et al.[23]	5	60g daily	7 days	A Double Blind, Placebo Controlled, Crossover Trial of D-Ribose in McArdles Disease.	Some diarrhea, occasional symptoms of hypoglycemia and light-headedness reported.
Zollner et al.[24]	1	60g daily	>1 yr.	Myoadenylate Deaminase Deficiency: Successful Symptomatic Therapy by High Dose Oral Administration of Ribose.	50-60 grams daily well tolerated without side effects.
Gross and Zollner[25]	8	82-130g	10 hrs.	Serum Levels of Glucose, Insulin and C-Peptide during Long-Term D-Ribose Administration in Man.	Decrease in glucose was asymptomatic.
Steinberg et al.[26]	34	15g	Single dose	Oral Administration of D-Ribose in Diabetes Mellitus.	Dissociation in the magnitude of the insulin response and the degree of hypoglycemia.

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16. Steinberg, T. et al., "The Effect of D-Ribose Infusion on Serum Immuno-Reactive Insulin and Glucose Concentration," Metabolism 16 (1967): 40-46.

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