DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date . MAR 12 1998

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

98 MAR 17 P1

Subject 75-day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

New Dietary Ingredient	Pinitol (2-O-methyl-1,2,4 cis-3,5,6 trans hexahydrooxycyclohexanol)
Firm:	Humanetics Corporation
Date Received by FDA:	December 9, 1997
90-day Date:	March 8, 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 March 8, 1998.

Robert J. Moore, Ph.D.

95S-0316

RPT 16

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

MAR 12 1998

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

Dear Mr. Zenk:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) dated December 1, 1997, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., Pinitol) was received by the Food and Drug Administration (FDA) on December 9, 1997. Your submission will be kept confidential for 90 days from the date of receipt, and after March 8, 1998, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Please contact us if you have questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

HUMANETICS
CORPORATION

December 1, 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 wishes to notify the Food and Drug Administration that it will market a new dietary ingredient, Pinitol, a natural and substantially pure inositol derived from pine bark. Accordingly, enclosed are two (2) copies of this notification.

The dietary supplement that contains Pinitol will consist of up to 250 milligrams of Pinitol for ingestion which will be suggested to be taken up 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 four-page safety profile summary of Pinitol with reference to published literature.

(2) Nineteen supporting references.

Sincerely,

Ronald J. Zenk
President & CEO

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Pinitol
(3-O-Methyl-1,2,4 cis-3,5,6 trans hexahydroxycyclohexanol)

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

Background

Pinitol is derived from pine trees and is a substantially pure preparation. Chemically, it is defined as an inositol. Inositols are a class of compounds which consists of nine distinct isomers.[1] Inositols resemble six member ring simple sugars (i.e. glucose) and are also called sugar alcohols. Inositols are natural ingredients found in all plants and animals and are essential for life. Inositols, like simple sugars, are a part of the normal human diet and similarly are also non-toxic.[1,2] Pinitol, which contains a methyl ether group at the three position, is found in high concentrations in certain legumes (eg. soy), plants and in pine tree components.[3,4] Both legumes and pine tree preparations have been safely consumed by humans (and other mammals) for centuries.

Pinitol has a hypoglycemic effect (i.e. an ability to lower blood sugar levels) which was first demonstrated in 1987.[5] More recently, others have confirmed in man that orally ingested pinitol enhances insulin function and lowers blood glucose.[3,6] As discussed below, safe doses of pinitol used in animal and human studies are generally in the range of 5-10 mg/kg. Pinitol intake in the normal diets of peoples of various Asian countries is also within this range.

Safety Assessments

Pinitol

Pinitol is a natural component of the normal human diet. For example, pinitol is present at about 1% dry weight in soy.[3] In Indonesia, about 2 million metric tons of soy were consumed in 1994 by a total population of 200 million.[7] This converts to an average intake of 25-30 grams of soy per day per person or about 250-300 mg of pinitol, which is about four mg/kg/day in a 70 kg individual. If the average weight of all individuals is adjusted downward to 25-50 kg to account for children in the population, then about five to ten mg/kg of pinitol per individual is consumed per day in Indonesia. This daily dose range of pinitol is therefore considered safe as evidenced by centuries of soy intake. In a like manner, a serving containing over 100 grams (about ¼ pound) of soy per day, which is a reasonable portion for some individuals, would provide about one gram of pinitol or a dose level of over ten mg/kg in a 70 kg individual. While crude soy preparations are not substantially pure and may not provide the most readily or rapidly assimilated form of pinitol, it is obvious that pinitol consumption through soy is substantial.

In alloxan-induced diabetic mice, chronic treatment of ten mg/kg of pinitol for three days (five doses) was administered safely.[5] In humans, 4.15 mg/kg/day of pinitol was given orally for three days to five non-insulin dependent diabetic subjects with no adverse safety effects noted.[3] Thus, by history of use, animal and human clinical scientific studies, pinitol (and inositols as a group) are non-toxic and safe in man.

Other Inositols

One of the isomers of pinitol (just as glucose is an isomer of galactose and mannose) is myoinositol, which is the most ubiquitous inositol in foods, with only different orientation

(stereochemistry) between two of the ring hydroxyl groups.[8] Myoinositol is non toxic, considered safe and is listed as a GRAS food ingredient.[1,2,9,10] However, myoinositol is generally acknowledged as being devoid of the hypoglycemic effects of pinitol or chiroinositol (a hydrolysis product or demethylated metabolite of pinitol).[3,9,11] In humans, doses of 20 grams/day of myoinositol for 14 days cause no adverse effects.[12] Additionally, levels of three grams/day (40 mg/kg/day) for 24 weeks[13] and six grams/day for eight weeks[14] of myoinositol were given safely to humans. In a monkey study, 1.5 grams/kg/day (equivalent to 105 grams/day in a 70 kg man) of myoinositol was given for five days.[9] These authors and others have shown that myoinositol can be converted to chiroinositol.[9,15] Similarly, pinitol can be converted to chiroinositol following an oral dose in humans.[3] Overall, existing literature demonstrates that inositols as a group are non-toxic and safe.

D-chiroinositol, the demethylated metabolite or chemical hydrolysis product of pinitol, is also safe. It is 1) found in food and other sources following isolation using strong chemical hydrolysis methods;[3,16] 2) excreted in high levels in human urine;[17,18] 3) found in blood following an oral pinitol dose;[3] and 4) a less active hypoglycemic than pinitol.[11] For example, a non-lethal intravenous dose of D-chiroinositol in monkeys is greater than one gram/kg.[11] Doses of 1.5 grams kg/day have been given to monkeys for five days without adverse effects.[9] This dose is equivalent to 105 grams per day in a 70 kg human.

Dose Considerations

Pinitol is the parent inositol found in high levels in certain plants, trees and foods that has a demonstrated blood glucose lowering and insulin function enhancing effect. Thus dietary

supplementation of pinitol may be recommended to help maintain normal metabolic function.[19] In scientific studies, pinitol has been given safely to both animals and man at levels of up to ten mg/kg/day. Therefore, an average 70 kg individual could safely consume 700 mg of pinitol per day as an oral dietary supplement. Accordingly, the recommended dose of a substantially pure pinitol preparation obtained from pine tree extracts is 200-250 mg taken up to four times per day depending on the individual's weight.

References

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