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Tagatose, the New GRAS Sweetener and Health Product

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ABSTRACT

Tagatose, a low-calorie, full-bulk natural sugar, has just attained GRAS (Generally Recognized As Safe) status under U.S. Food and Drug Administration (FDA) regulations, thereby permitting its use as a sweetener in foods and beverages. This paper presents all current aspects of tagatose with respect to demonstrated food and beverage applications and the potential health and medical benefits of this unique substance. Summarized studies are referenced to detailed peer-reviewed papers. The safety studies followed the recommendations in the FDA "Red Book." Results were submitted to an Expert Panel for determination of GRAS status under FDA regulation. Small phase 2 clinical trials showed tagatose to be effective in treating type 2 diabetes. The results, buttressed by the references cited, support the efficacy of the various applications disclosed for tagatose. Tagatose has been found to be safe and efficacious for use as a low-calorie, full-bulk sweetener in a wide variety of foods, beverages, health foods and dietary supplements. It fills broad, heretofore unmet needs for a low-calorie sweetener in products where the bulk of sugar is important, such as chocolates, chewing gum, cakes, ice cream and frosted cereals. Its synergism with high-intensity sweeteners also makes it useful in sodas. Various health and medical benefits are indicated, including the treatment of type 2 diabetes, hyperglycemia, anemia, and hemophilia and the improvement of fetal development.

INTRODUCTION

Since D-tagatose was first described five years ago¹, its story has grown dramatically. This naturally occurring, simple sugar, hereinafter called "tagatose," has now been successfully formulated in a variety of products. Most importantly, this versatile product has now been established² as GRAS (Generally Recognized as Safe) for use in foods and beverages as the result of an extensive review of its safety.

In addition to its originally planned use as a sweetener in foods, surprising new beneficial uses in health and medicine have been discovered, with no toxic manifestations. Earlier in 2000, tagatose achieved GRAS status for passive use as a sweetener in drugs and in cosmetic products³. And shortly thereafter, tagatose was determined to be GRAS⁴ for use in pharmaceutical products for canines and nonhuman primates. All regulatory hurdles have now been cleared for the beneficial food and beverage uses of this simple, naturally occurring sugar. Active drug uses will require further development.

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BACKGROUND

The need for low-calorie sweeteners has been evident for many years, but the emphasis has grown recently with the accelerating trend toward obesity in the developed nations. Following the lead of body stylists, consumers equate slimness with health and glamour. Thus, both health and body image drive the market for low-calorie sweeteners. The earliest low-calorie sweeteners, beginning with the serendipitous discovery of saccharin,^{*} were of the high-intensity type, hundreds of times sweeter than sucrose. Although the U.S. Food and Drug Administration (FDA) declared it carcinogenic, saccharin was in such demand that the U.S. Congress consistently overrode the FDA's efforts to ban it. But when the FDA questioned the safety of cyclamates in the 1960s, successfully banning them as carcinogens in 1970, the spotlight focused on the safety of substitute sweeteners. It is probable that no other food additives have been subject to such suspicion and excruciating proof of safety.

But safety was not their only marketing impediment. Because of their intense sweetness, their use is limited to replacing the sweetness of sugar in products where sugar's bulk is not needed. With beverages, for example, in which the bulk is water, a tiny pinch of the substitute sweetener does the job. Cakes and ice creams, on the other hand, need sugar's bulk. If a high-intensity sweetener were to be used, a low-calorie bulking agent would have to be added, but cost and off-flavor qualities have limited the use of bulk substitutes.

The market needed a safe, full-bulk, low-calorie sweetener. Cognizant of this, scientists from Spherix Incorporated, while engaged in chiral carbohydrate research, conceived of using L-sugars as sweeteners⁵. They theorized that L-sugars would not be metabolized because their chirality is the opposite of that required for digestion. But would they be sweet? The then accepted explanation of the taste mechanism, based on presumed enzymatic sensing reactions, predicted that L-sugars would not be sweet. But when Spherix had L-glucose prepared in high purity, sensory tests found it to be as sweet and to taste the same as D-glucose.

After identifying L-glucose as a potential full-bulk sweetener, we set out to determine its caloric content to verify our chiral theory. In-house tests at Spherix Incorporated¹ indicated that animals fed glucose derived little, if any, caloric value from it. We then sought the renowned expertise of the U.K. Agricultural and Food Research Council Institute of Food Research to confirm this result. There, complete body calorimetry tests showed that rats achieved no net gain in energy from ingesting L-glucose; indeed, a small deficit was seen⁶. Therefore, it was concluded that any metabolism of L-glucose required as many or slightly more calories than the L-glucose provided.

Spherix then synthesized L-glucose and a number of the L-hexoses. Although taste and caloric test results showed that several were good low-calorie sweetener candidates, economical means for their production have eluded us.

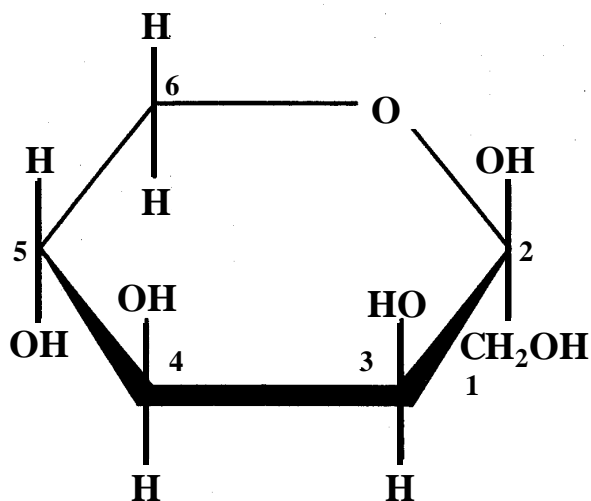
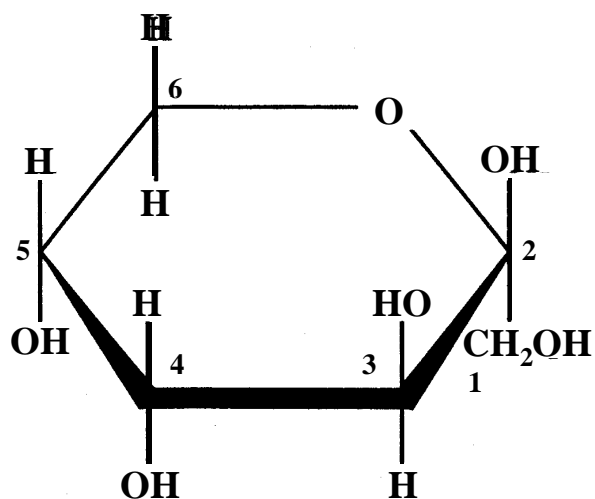
^{*} Discovered by Ira Remsen in 1879 as a research assistant exploring ways to preserve foods at The Johns Hopkins University, where he later became president.

TAGATOSE

Identification as a candidate

While the L-sugars remain candidates for low-calorie sweeteners and other applications, in the early 1990s Spherix shifted its emphasis to tagatose. Because the six-carbon sugar, tagatose, is an L-epimer of D-fructose (Fig. 1), we suspected that tagatose might behave like L-fructose, which exhibited excellent characteristics as a low-calorie sweetener. First, we synthesized some tagatose and tested its sweetness. Tagatose proved virtually indistinguishable in taste from sucrose, but with a slightly quicker sweetness onset, similar to that of fructose. It is 92% as sweet as sucrose when both are tested in 10% aqueous solutions. No cooling effect is detected.

Figure 1: The Molecular Structures of D-Tagatose and D-Fructose



The next step was to assess the caloric value of tagatose. Rat test data⁷ showed it to yield few, if any, calories, supplying virtually no net available energy. This important finding spurred us on, and soon we invented an economical way to produce tagatose. Because it uses no organic solvents and yields no toxic or nonbiodegradable wastes, the process is quite benign, or “friendly,” from the standpoints of environment and health.

Table 1 shows the key properties of tagatose.

TABLE 1. KEY PHYSICAL, CHEMICAL, AND BIOLOGICAL PROPERTIES OF TAGATOSE

<i>Property</i>	<i>Value/Comment</i>
Common names	D-Tagatose, Tagatose
Synonym	D-lyxo-hexulose
Molecular formula	C ₆ H ₁₂ O ₆
Chemical family	Carbohydrate; monosaccharide; ketohexose
Structure	Contains 3 chiral carbons; C-4 epimer of D-fructose
Molecular weight	180
CAS No.	87-81-0
Physical form	White anhydrous crystalline solid
Odor	None
Melting point	134°C
Decomposition temperature	120°C
Optical rotation	$\alpha_D^{20} = -5^\circ$ (c = 1 in H ₂ O)
Solubility (in H ₂ O)	58% wt/wt at 21°C
pH stability range	2-7
Relative sweetness	92% of sucrose when compared in 10% solutions
Sweetness profile	Emulates sucrose, but with faster onset like fructose
Cooling effect	None
Caloric value	1.5 kcal/g approved: ≤ 1.4 kcal/g (reported range: -0.12-1.4 kcal/g)
Cariogenicity	None
Flavor enhancer	Synergistic with high-intensity sweeteners
Health promotion	Low calorie, prebiotic, low glycemic, no elevation of blood glucose, suitable for diabetics, healthy foods, dietary supplements, beneficial drugs or drug adjuvants, antioxidant, cytoprotective
Bulk	Similar to sucrose
Humectant	Similar to sorbitol
Hygroscopicity	Less than fructose
Metabolism	Absorbed ~25%: only normal metabolic products produced. Unabsorbed ~75%: unless and until adapted, laxation at high doses
Maillard and caramel reactions	Browns like sucrose
Initial products	Chocolate candy, soft confectioneries, hard confectioneries, diet soft drinks, ready to eat cereals, frosting, ice cream, frozen yogurt, diet chewing gum
Regulatory status	Excipient in drugs and nonfoods—GRAS; excipient use in animal feeds—GRAS; sweetener use in foods—GRAS

Metabolism of tagatose

Rats given radiolabeled tagatose metabolized only 15% to 20% of the tagatose they absorbed across the small intestine.⁷ Absorbed tagatose is fully metabolized to CO₂ and H₂O, a metabolic fate similar to that of glucose and other monosaccharides. Evidence shows that, although the metabolic steps are the same, the rate of metabolism of tagatose is slower than for related sugars such as fructose.

Most of the tagatose ingested is not absorbed through the small intestine but passes to the lower gut, where it is fermented by the bacteria there. This was demonstrated by the fact that rats with normal levels of gut microflora excreting 93% less tagatose in their feces than did germ-free rats⁷. Short-chain fatty acids, carbon dioxide, hydrogen, and methane are the products of this intestinal fermentation⁷. The short-chain fatty acids are largely reabsorbed into the bloodstream.

Early product development

Early bench-scale production provided enough tagatose to develop chocolates and chewing gum, both normally composed of 50% to 60% sucrose. The products were prepared under contract to a food products development company,^{*} with Spherix supplying the tagatose to the specifications in Table 2. The targeted chocolates were a popular brand of milk chocolate and dark chocolate, and the targeted chewing gum was a popular, spearmint-flavored brand. Formulations proved to be relatively straightforward—essentially one-to-one replacements of sucrose. Both the chocolate candies and the gum closely emulated the sensory and physical properties of their targets.

Safety

We then began the long task of establishing safety. Following the recommendations of the FDA's "Red Book," we performed a number of the cited animal tests. No toxic effects were found. To establish third-party independence, we contracted further studies to industrial toxicology laboratories. The test program was carried out under the direction of a professional consulting toxicologist^{**} retained for the purpose. This work, which was completed in about 3 years, included methods recommended as more sensitive than the traditional carcinogenicity tests: the Ames salmonella mutation test, the mouse lymphoma mutation test, an *in vitro* test with Chinese hamster ovary cells, and an *in vivo* mouse micronucleus test. Tagatose produced no toxic events. Acute oral toxicity studies, dermal irritation and allergic contact sensitization, and sub-chronic toxicity studies all showed no toxic effects. The product development and safety data prompted manufacturers of food ingredients and products to seek rights to our extensively patented technology.

^{*} Hammond and Associates, John Hammond, President, formerly Director of New Product Technology for General Mills, currently Product Development Chemist with the Wrigley Company, performed the work.

^{**} Robert Weir, deceased.

Licensing of food use

In early 1997, we executed a license agreement with MD Foods Ingredients, a Danish dairy food products company (since merged into, and henceforth called, Arla Foods) that was interested in expanding its line of products. Arla Foods was especially interested in tagatose because the basic raw material, de-proteinated whey, is a large, low-value by-product of the company's cheese-making process. Spherix's scientists and engineers visited Denmark and helped set up a pilot plant to produce tagatose according to our process. Spherix then undertook a 2-year technology transfer program. Arla Foods manufactured enough tagatose to develop a number of products as it explored potential customers in the food product industry.

TABLE 2. D-TAGATOSE PRODUCT SPECIFICATIONS

<i>Type</i>	<i>Specifications</i>	<i>Value</i>
Physical	Appearance	White crystal
	Melting point	132°-135°C
	Ash	<1,000 ppm
	Solubility (in water)	58% (wt/wt)
Microbiology	Total plate count	<10,000/g
	Coliforms	<10/g
	Mold/Yeast	<10/g
	Staphylococcus	neg. in 1 g
	Salmonella	neg. in 100 g
Sugars	D-Tagatose	≥99% (wt/wt)
	D-Galactose	≤0.5% (wt/wt)
	Other sugars	≤0.5% (wt/wt)
Heavy Metals	Silver	<0.5 ppm
	Arsenic	<0.5 ppm
	Barium	<1 ppm
	Cadmium	<0.1 ppm
	Chromium	<0.5 ppm
	Copper	<1 ppm
	Mercury	<0.2 ppm
	Manganese	<0.5 ppm
	Nickel	<0.5 ppm
	Lead	<0.1 ppm
	Antimony	<0.1 ppm
	Selenium	<10 ppm
Other	Protein content (N X 6.25)	≤0.2% (wt/wt)

Caloric value

When tagatose became a serious candidate, the U.K. Agricultural and Food Research Council Institute of Food Research was asked to make the same caloric determination on it as it had made on L-glucose. The findings⁸ showed a negative net value of 0.12 Kcal/g. After that, Arla Foods had studies made using the pig as a model for humans to obtain an available caloric value for tagatose. Not being able to perform bomb calorimetry on the *in vivo* studies with pigs,

the experimenters applied a factorial method⁹ to the discrete sample analyses. The metabolizable energy was reported to range from 1.1 to 1.4 Kcal/g, and, depending on the experimental procedure, the interpretation of results, and the factors applied, it could be estimated lower. Conferring with potential corporate customers and taking a conservative approach that still left the product desirable, Arla Foods requested the FDA to approve a caloric value of 1.5 Kcal/g.¹⁰ The FDA responded with a “no objection” letter. The submittal to the FDA, however, pointed out that future requests, supported by pertinent studies, may be made to reduce the allowed caloric value.

REGULATORY APPROVAL FOR FOOD USE

Current exposures to tagatose

An extensive analytical survey of various foods showed that many people around the world ingest small amounts of tagatose in dairy products such as sterilized, ultra-high-temperature and powdered milk, hot cocoa, various cheeses, certain kinds of yogurt, infant formula, and some relatively rare edible vegetation. Concentrations in such foods are extremely low, ranging from 4 mg/kg food item in Similac® infant formula to 800 mg/kg food item in powdered cow’s milk and 6,500 mg/kg in medications. Hundreds of thousands of people have now been chronically exposed to tagatose in two common drugs, Chronulac® (beginning in 1976) and Cephulac® (1983), and their generic equivalents. Known current occurrences of tagatose are summarized in Table 3.

Expert Panel on tagatose

Arla Foods decided to seek regulatory approval for the use of tagatose in foods, first in the United States and then in Europe and elsewhere. The U.S. FDA-approved method of appointing an Expert Panel to review data that, in the traditional petition route, would have been reviewed by the FDA itself was the route chosen. This approach saves time by allowing the company to self-affirm a product as GRAS for specific uses if the Expert Panel finds it safe for the proposed uses. Accordingly, Arla Foods commissioned a panel of international experts in the field of sweetener safety and submitted all studies on tagatose to this Expert Panel. On the advice of an industrial toxicology consulting firm*, the company conducted several additional studies that went beyond those recommended by the FDA Red Book. Even though none of the previous studies had shown any toxic effect of tagatose, these additional studies were done to foresee and satisfy any future questions that might arise about the product’s safety. These investigations, like the earlier ones, found no evidence of toxicity.

At the same time as these studies were being completed, Spherix, exploring drug uses for tagatose, contracted for studies (described later) in which large amounts of tagatose were fed to human subjects daily. Because the FDA food additive investigations require no tests on humans, these studies afforded perhaps the best direct insight into the safety of tagatose for humans. No toxic incidents were detected. All of the data, reports, and summaries on these human studies were submitted to the Expert Panel in addition to the studies performed under FDA Red Book guidance.

* Bioresco, Basel, Switzerland.

While the material on safety was being prepared, experiments were conducted by Arla Foods to select foods suitable for an early introduction of tagatose. Part of the data package for the Expert Panel on GRAS included the projection of average daily intakes for such specific products projected to be consumed by various segments of the population. Any interplay or addition of these consumptions were taken into account in proposing total daily intake levels to the Expert Panel. To help estimate daily intake levels, Arla Foods had human acceptance/tolerance tests performed. The individual amounts of tagatose proposed for specific products and the limit on the total amount to be ingested are consonant with the results of these tests. Increasingly excessive consumption leads to mild intestinal discomfort, flatulence, laxation and, ultimately, diarrhea. These are the same effects produced by consumption of any sugar, including sucrose, although greater tolerance is shown for the latter.

TABLE 3. OCCURRENCE OF D-TAGATOSE IN FOODS AND DRUGS

<i>Food</i>	<i>Concentration (mg/kg)</i>	<i>Reference</i>
Sterilized cow's milk	2 to 3,000	Troyano et al., 1991 ¹¹ , 1992 ¹²
Hot cocoa (processed with alkali) prepared with milk	140-1,000	Biospherics Incorporated ¹
Powdered cow's milk	800	Richards and Chandrasekhara, 1960 ¹³
Similac® infant formula	4	Biospherics Incorporated internal report
Enfamil® infant formula	23	Biospherics Incorporated internal report
Parmesan cheese*	10	Biospherics Incorporated internal report
Gjetost cheese*	15	Biospherics Incorporated internal report
Cheddar cheese*	2	Biospherics Incorporated internal report
Roquefort cheese*	20	Biospherics Incorporated internal report
Feta cheese*	17	Biospherics Incorporated internal report
Ultra high temperature milk	~5	Biospherics Incorporated ¹
BA Nature® Yogurt	29	Biospherics Incorporated internal report
Cephular®, an orally-ingested medication for treatment of portal-systemic encephalopathy	6,500	Parrish et al., 1980 ¹⁴
Chronulac®, an orally ingested laxative	6,500	Parrish et al. 1980 ¹⁴
Tropical date tree, <i>Sterculia setigera</i> , exudates	30% of sugar	Biospherics Incorporated ¹
Common metabolite from various <i>Lactobacilli</i> and dairy <i>Streptococcus</i>	Variable range to be determined	Biospherics Incorporated ¹
Lichens, <i>Rocella hypomecha</i> , <i>Rocella linearis</i> and <i>Rocella fuciformis</i>	Not applicable	Biospherics Incorporated ¹

*Estimates derived from extrapolation below the calibration curve.

Arla Foods, its consultants, and the Expert Panel cooperated to assemble all the requirements for a full review by the Expert Panel. The review process took approximately 2 years with considerable interaction among the Expert Panel, the company, and its consultants, until, on April 11, 2001, the Panel issued its opinion that tagatose qualified as GRAS for the uses intended in foods and beverages.

PROCESS DEVELOPMENT

The patented process developed for the manufacture of tagatose by Spherix starts with lactose derived from whey or deproteinized whey. Should economics dictate, food-grade lactose may be purchased for the starting point. The lactose is solubilized and subjected to enzyme-catalyzed hydrolysis, yielding a mixture of D-galactose and D-glucose. The products are separated chromatographically, and the galactose is isomerized with lime in the presence of a catalyst to form a patented intermediate, calcium tagatate. Removed from the reaction mixture, the calcium tagatate is then treated to yield tagatose that is purified by chromatography. The tagatose is concentrated and dried into crystalline form. No organic solvent is used in the process, which makes it fairly easy to clean up the product. The specifications for the resulting product remain as shown in Table 2.

DRUG AND NON-FOOD USES

Type 2 diabetes

Beyond its benignity and its incidental health benefits, tagatose has been found to have a surprising number of drug attributes against diseases and poor health. These findings result from Spherix's pursuit of nonfood uses of tagatose, for which the Company retains the rights. In an early investigation of the influence of tagatose on blood glucose levels, we conducted experiments on normal and genetically diabetic rats.¹⁵ Tagatose was shown not to increase glucose levels, and, in addition, the sugar was found to be antihyperglycemic.¹⁶ Even more surprisingly, these studies found that tagatose relieved the symptoms of diabetes in the diseased animals.¹⁷ Accordingly, human clinical trials were then instituted on patients with type 2 diabetes and normal persons at the Department of Endocrinology at the University of Maryland School of Medicine.¹¹ The subjects ingested 75 g tagatose or sucrose each day for 8 weeks. Tagatose produced no change in fasting glucose or insulin levels. In addition, pre-treatment with tagatose attenuated the rise in serum glucose after oral glucose intake. These findings¹⁸ prompted further research,¹⁹ which concluded, "d-Tagatose may be a useful therapeutic adjunct in the management of type 2 diabetes mellitus." A small clinical trial was then conducted as a follow-up. After a 2-month run-in period, patients with type 2 diabetes were given 15-g doses of tagatose in each of three daily meals for 1 year. The study confirmed and extended the usefulness of tagatose in treating the disease and found that initial gastrointestinal side effects were mild and generally ameliorated after about the second week of treatment. Details of this study should soon appear in a paper²⁰ that has been submitted for publication.

Antihyperglycemic agent

Hyperglycemia is generally recognized as the major cause of aging. The glucose-induced linking of protein molecules in muscle and brain causes those organs to atrophy. As stated earlier, tagatose has been found to be antihyperglycemic. It may develop that prescribed doses of tagatose, perhaps as part of a dietary restriction program, promote healthier, more active and longer lives.

Controlled weight loss

Both type 2 diabetics and normal subjects receiving the daily regimen of tagatose for 12 months gradually and consistently lost weight at medically desirable rates¹⁶. A prescription for controlled weight loss may be determined by titrating the dosage to the individual patient under a physician's care.

Pregnancy and fetal development

Examination of the rat studies on the safety of tagatose summarized in Kruger et al.²¹ revealed that female rats on a tagatose diet showed a higher percentage of pregnancies than did the control rats. Moreover, the rats receiving tagatose produced a higher percentage of live births than did the control rats. In addition, the tagatose-fed females delivered heavier fetuses, although within the normal neonatal weight range, than did their controls.²²

Blood factors

Analysis of other data from the rat feeding and safety studies, summarized in Kruger et al.,¹⁷ showed that male rats receiving tagatose developed higher red blood cell counts than did their controls, suggesting possible usefulness of tagatose in treating anemia. The same study noted that tagatose-fed rats of both sexes showed improvement in other blood factors that would prove beneficial in the treatment of hemophilia. The prothrombin time decreased, as did the activated partial thromboplastin time. These favorable results were attended by increased fibrinogen levels.²³

Organ transplants

Another application discovered for tagatose augers well for its safety. As it removes foreign substances from the blood, the liver is exposed to the toxic substances accumulated. Accordingly, the GRAS research included a concentrated effort to study possible adverse effects of tagatose on the liver. Biospherics cooperated in a study to determine the effects of tagatose on liver hepatocytes. In addition to investigating the toxic effects that might be manifested by cultured rat hepatocytes exposed to tagatose, the study sought to determine whether tagatose might affect liver cells exposed to strong toxins. The possibility existed that tagatose might make the cells more susceptible to such toxins. The studies^{24,25} produced a surprising result: tagatose showed powerful antioxidant and cytoprotective effects that protected the liver cells from the lethal pro-oxidant poisons cocaine and nitrofurantoin. Control cells that lacked tagatose protection died. This protective action of tagatose was welcome news with respect to assuaging any potential human liver concerns. If tagatose protects liver cells *in vitro*, it would seem unlikely to damage them *in vivo*. But the data indicated yet another use for tagatose—to protect the liver, or other transplanted organs, when excised, stored, and implanted into humans. A patent was received for this innovative use of tagatose.

Further analysis of the test data on tagatose has revealed another significant potential drug use for this unique and versatile material, increasing HDL blood levels.

NONFOOD, NONDRUG USES

Nonfood, nondrug uses have also been found for tagatose. On July 1, 2000, a determination was made that tagatose is GRAS³ for each of the following uses:

Low-calorie sweetener in nonchronic drugs

The unpleasant taste of many prescription drugs makes it difficult for children and even adults to take them. To overcome this problem, pharmaceutical companies have added either caloric or noncaloric sweeteners to a number of such medications. The excellent taste and low caloric value of tagatose makes it a good candidate for such excipient use in drugs. Applications for tagatose in nonchronic prescription medications for children and adults were investigated. Table 4 shows such use of tagatose in throat lozenges, over-the-counter (OTC) drugs, and diabetic cough syrup, with the derivation of appropriate estimated daily intakes (EDI) for adults. Similar assessments of the EDIs established for chewable antibiotic tablets and non-steroidal anti-inflammatory drugs (NSAIDs), all excipient uses for pediatric drugs, are shown in Table 5. In both cases, requested EDIs were allowed. Inasmuch as these uses are all nonchronic in nature, they should have no impact on the EDI approvals sought for food uses.

TABLE 4. APPROVED ESTIMATED DAILY INTAKE OF D-TAGATOSE USED AS AN EXCIPIENT IN HUMAN ADULT DRUG PRODUCTS

<i>Drug product</i>	<i>D-Tagatose content</i>	<i>No. daily doses</i>	<i>EDI (60-kg adult)</i>	
			<i>(g/day)</i>	<i>(g/kg/day)</i>
Throat lozenges	0.25 g/lozenge	Up to 24 lozenges	6	0.1
OTC drugs (effervescent cold medicine)	1 g/tablet	Up to 8 tablets	8	0.13
Diabetic cough syrup	0.67 g/tsp	Up to 12 tsp	8	0.13

TABLE 5. APPROVED ESTIMATED DAILY INTAKE OF D-TAGATOSE USED AS AN EXCIPIENT IN HUMAN PEDIATRIC PRODUCTS

<i>Drug product</i>	<i>D-Tagatose content</i>	<i>No. daily Doses</i>	<i>EDI (11.4-kg adult)</i>	
			<i>(g/day)</i>	<i>(g/kg/day)</i>
Chewable flavored antibiotic tablets	81 mg/tablet ^a	1.5 tablets	0.122	0.011
Pediatric oral antibiotic drops	0.4 g/ml ^f	4.5 ml	1.8	0.16
Children's chewable OTC NSAID drug	0.125 g/tablet	Up to 8 tablets	1.0	0.088
Children's OTC NSAID suspension cold and flu formula	0.05 g/day	Up to 20 ml	1.0	0.088
Total EDI ^b			2.8	0.25

(a) Amount estimated to achieve the same sweetness as sucrose (sucrose is 1.08 times sweeter than D-tagatose).

(b) Based on the assumption that a child prescribed an antibiotic could also be given an OTC cold or flu medication. As a conservation estimate, the higher of the two EDIs associated with intake of an antibiotic (i.e., pediatric oral antibiotic drops) was used.

Toothpaste, mouthwash, cosmetics

Tagatose also has potential cosmetic uses. It may be substituted for sucrose and other sweeteners in toothpaste, mouthwash, and lipstick. Fully acceptable products have been formulated for each such use as confirmed in organoleptic tests. A key requirement for use in toothpaste is humectancy. Experiments²⁶ have shown the humectancy of tagatose to be satisfactory for use in toothpaste. Its humectancy compares well with that of the widely used toothpaste ingredient sorbitol. Table 6 shows the GRAS-approved uses of tagatose in these products for adults and children.

TABLE 6. APPROVED ESTIMATED DAILY INTAKE OF D-TAGATOSE USED AS AN INGREDIENT IN COSMETIC PRODUCTS^(A)

<i>Cosmetic product</i>	<i>D-Tagatose content</i>	<i>Assumed use conditions</i>	<i>EDI (60-kg adult)</i>		<i>Child (11.4-kg)</i>	
			<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Toothpaste ^a	55%	Child age 2-4 yr: 0.82 g toothpaste ingested with each brushing ^b Adult age 20-35 yr: 0.13 g toothpaste ingested with each brushing ^b	0.21	0.0035	1.4	0.12
Mouthwash	35%	25 ml per rinse; 3 times per day; approximately 10% of mouthwash ingested with each rinse ^c ; density of mouthwash is assumed to be the same as water (1 ml = 1 g)	2.6	0.043	NA	NA
Flavored lipstick	30%	10 mg lipstick applied per application; 10 applications per day; all lipstick applied is assumed to be ingested	0.03	0.0005	NA	NA

NA, not applicable.

^a Fluoride-containing toothpaste is considered a drug product; the EDI of D-tagatose from fluoride and non-fluoride-containing toothpaste is assumed to be the same.

^b Barnhart, et al., 1974²⁷ (95th percentile estimate).

^c Barnhart, et al., 1974, from data for toothpaste use (0.13 g ingested per brushing X 1.39 g mean amount applied per brushing = 10% ingested) assumed to apply also to mouthwash as a conservative estimate.

GRAS basis

The rationales for all of the nonfood, nondrug uses of tagatose are described in *GRAS Determination for D-Tagatose as a Sweetener in Drugs and Cosmetic Products*.³ That report explains the safety evaluation as follows:

Safety Evaluation

Evaluation of the safety of D-tagatose is accomplished through a review of the extensive database on the safety of D-tagatose, including history of human exposure, animal and human studies, and a comparison of the current AIL (Acceptable Intake Level) to the EDI (Estimated Daily Intake) of D-tagatose. If the EDI is less than (or approximates) the AIL, then the proposed use can be considered to be safe.

The EDI of D-tagatose associated with its proposed use as an excipient in limited and repeated exposure pediatric drugs (assuming a child body weight of 25 lbs or 11.4 kg) is 2.8 g/day, or 0.25 g/kg/day. The EDI of D-tagatose associated with its proposed use as an excipient in limited and repeated exposure adult OTC drug products should not exceed 14 g/day, or 0.23 g/kg/day assuming a 60-kg adult body weight. The EDIs for D-tagatose from use of pediatric and adult drug products reflect the conservative assumption that more than one drug product containing D-tagatose could be taken concurrently; EDIs from the use of a single drug product would be less. The EDI of D-tagatose associated with proposed uses in cosmetics was evaluated for both child and adult use. The EDI for a child's use of toothpaste is 0.12 g/kg/day (1.4 g/day for an 11.4-kg child). The EDIs for adult use of toothpaste, mouthwash, and flavored lipstick range from 0.0005 to 0.043 g/kg/day (0.03 to 2.6 g/day). The EDIs derived from drug use of D-tagatose are not combined with the EDIs from use in cosmetics because D-tagatose consumption from drug use is short-term and occasional.

Human clinical studies of D-tagatose, as well as data from experimental animal studies, indicate that D-tagatose intake at levels of up to 15 g/day in the adult, equivalent to a dose of 0.25 g/kg/day (assuming a 60-kg adult body weight), is well tolerated and without reported adverse health effects. It can thus be concluded that the AIL for consumption of D-tagatose as an excipient in drugs and as an ingredient in cosmetics is up to 15 g/day (0.25 g/kg/day) for a 60-kg adult. The AIL for consumption of D-tagatose by children as an excipient in drugs and as an ingredient in cosmetics is up to 0.25 g/kg/day (e.g., 2.8 g/day for an 11.4-kg child). This AIL, extrapolated from the AIL for an adult, is conservatively based on the assumption that tolerance is directly related to body weight.

Comparison of the AIL to the EDIs reveals that the EDIs for the proposed uses of D-tagatose in pediatric drug products (0.25 g/kg/day or 2.8 g/day for a 11.4-kg child), adult OTC drug products (0.23 g/kg/day or 14 g/day), cosmetic products used by children (0.12 g/kg/day or 1.4 g/day for an 11.4-kg child), and cosmetic products used by adults (0.0005 to 0.043 g/kg/day or 0.03 to 2.6 g/day) do not exceed the AIL of 0.25 g/kg/day.

Based on the above evaluation, we conclude that the use of D-tagatose as a reduced calorie sweetener and bulking agent in drugs and in cosmetic products would not be expected to produce any acute or chronic adverse effects in individuals consuming these products. Evaluation of the safety of D-tagatose ingested for these uses was accomplished through a review of the extensive database on the safety of this product, including its gastrointestinal and systemic effects, animal and human studies, and a comparison of the current AIL to the EDIs for D-tagatose. Based on human tolerance, the AIL for D-tagatose of 15

grams/60 kg adult/day (or 0.25 grams/kg body weight/day for children and adults) should not be exceeded by the proposed uses.

The reviewing scientists determined that tagatose was GRAS for the specific uses and amounts stated in Tables 4, 5, and 6.

Subsequently, the FDA signed a “no objection” letter showing 30 g/day to have no adverse effect.

Sweetener in animal pharmaceuticals

Tagatose has just been determined to be GRAS for use as a sweetener in pharmaceutical products for canines and non-human primates.⁴ The same problem afflicting human subjects who must take unpleasant-tasting medicines also prevails for animals. Drugs are given to a wide range of mammals, including primates used in health and safety studies, industrial animal husbandry species, and pets. The stress of inducing an unwilling animal to ingest foul-tasting substances can be overcome by use of tagatose as an excipient. The low caloric value of tagatose may also enhance its usefulness in improving these products for overweight companion animals and for research animals under test regimens for diabetes or other illnesses. The latter use of tagatose could prevent complications that might alter the research results. The approved uses and EDIs are given in Table 7.

COST OF PRODUCTION

Optimizing our patented process for manufacturing tagatose has progressed over the more than 2 years that the pilot plant has been in operation. This process uses much of the same technology that is used to manufacture high fructose corn syrup (HFCS). The starting product, however, is whey or lactose (derived from whey) instead of the corn or glucose used for HFCS. Essentially the same manufacturing costs are projected for tagatose as for HFCS, plus the additional cost of the raw material for tagatose over that for HFCS. The ultimate cost will depend on the cost of the raw materials, the size of the production plants, and any further optimization achieved. Marketing studies and direct contact with food product manufacturers indicate that the product would enjoy strong acceptance at projected prices.

PRODUCT MARKETING STRATEGY

Food and beverage products

Arla Foods has designed its first full-scale tagatose production plant to be constructed at one of its dairy products facilities in Denmark. Arla Foods plans to sell tagatose directly to food product manufacturers. Tagatose has already been introduced to a number of prominent food product companies which have manufactured their current products and new products with it and have received it well. These include manufacturers of chocolate candy, soft and hard confectioneries, ready-to-eat cereals, ice cream and other frozen deserts, frostings, and chewing gum.

TABLE 7. APPROVED ESTIMATED DAILY INTAKE OF D-TAGATOSE USED AS A SWEETENER IN DRUG PRODUCTS FOR CANINES AND NON-HUMAN PRIMATES

<i>Drug product</i>	<i>D-Tagatose content</i>	<i>No. daily doses</i>	<i>EDI (11.4-kg dog)</i>	
			<i>(g/day)</i>	<i>(g/kg/day)</i>
Amoxicillin oral ^a suspension	0.40 g/ml	2 X 2.26 ml	1.8	0.16
Chewable amoxicillin ^b tablets	0.081 g/tablet	2 tablets	0.162	0.014
Chewable Baytril ^c tablets	0.25 g/tablet	3 tablets	0.75	0.066
Chewable Flagyl ^d tablets	0.5 g/tablet	4 tablets	2.0	0.175

(a) Amoxicillin suspension is manufactured by SmithKline Beecham as Amoxil®, 250 mg amoxicillin/5 ml.

(b) Amoxicillin tablets are manufactured by Apothecon, a subsidiary of Bristol-Myers Squibb, as Trimox®, 125 mg of amoxicillin/tablet

(c) Manufactured by Bioserve® Medicated Dosing Systems as 20 mg of Baytril/tablet

(d) Manufactured by Bioserve® Medicated Dosing Systems as 100 mg of Flagyl/tablet

More recently, manufacturers of diet soft drinks have shown interest, opening a large, unanticipated market. Although the cost differential between high-intensity sweeteners and tagatose (on a sweetness-to-sweetness basis) seemed to preclude using tagatose in soft drinks, this has turned out not to be the case. Arla Foods discovered²⁸ a synergism between tagatose and high-intensity sweeteners in which less than 1% of tagatose is required to effect a substantially improved flavor and mouthfeel of diet sodas. This has changed the cost paradigm. Applying tagatose in this way may overcome the objections consumers have about poor taste, which are believed responsible for the flattened growth curve of diet sodas over recent years.

Health foods

Arla Foods also discovered²⁹ that tagatose has prebiotic properties that improve digestion. Long appreciated in Europe and Asia, prebiotic properties are of growing interest in the United States. Tagatose selects for more favorable or benign microbial flora in the intestine and against potentially pathogenic organisms such as *Escherichia coli*. Moreover, tests have shown that ingestion of tagatose produces larger amounts of desirable short-chain fatty acids, in particular butyrate, than are produced by a normal diet. The beneficial effects of butyrate, including a defense against colon cancer, have been cited in the literature³⁰.

More recently, Arla Foods found that tagatose can improve the taste of health bars³¹ while adding to the health benefits of this increasingly popular part of many health and diet regimens. Other beneficial health uses for tagatose could support a variety of dietary supplements. These include use of tagatose to make low-glycemic breads, its antihyperglycemic properties, and its safe tolerance by diabetics.

Separate markets

Arla Foods has stated that tagatose for food use will be sold only as an ingredient for manufactured food products. The sweetener will not be retailed in bulk by itself. This strategy is key to our licensee's marketing plan to maintain complete control over the use of tagatose in food products and prevent it from being misapplied. This strategy fits nicely with marketing of tagatose in the nonfood uses, particularly pharmaceuticals. As a pharmaceutical, tagatose will be available only under prescription. It would not be practical for the public to obtain prescription amounts of tagatose in food products by eating, for example, multiple candy bars or huge amounts of ready-to-eat cereal. Although tagatose doses would generally be large compared to doses of most drugs, tagatose doses would offer no problem to the patient. Tasting like sugar, relatively large amounts of tagatose could be consumed in fruit juice, cereal, or any other desired food.

Separate marketing efforts are planned for the use of tagatose as an excipient in drugs and cosmetic products. It is expected that GRAS status can readily be obtained for the addition of tagatose as an excipient to pharmaceuticals already approved. A new market study³² shows that the use of sorbitol, for which tagatose can compete, is approximately \$1 billion per year.

Obviously, the drug uses of tagatose must be explored in much greater detail, culminating in extensive clinical trials and the full route required for FDA approval of a new drug. To accomplish this, Spherix is seeking a collaborative effort with a major pharmaceutical company.

POTENTIAL ECONOMIC AND HEALTH IMPACTS

An early market analysis³³ showed a worldwide multibillion dollar annual market for an "ideal, low-calorie, full-bulk sweetener." We believe that tagatose qualifies in many respects. A more recent study commissioned by Arla Foods and directed specifically at tagatose confirmed a potential market in foods in the billions of dollars per year. The additional potential uses in diet sodas, healthy food bars, and dietary supplements discovered since those market analyses were performed could expand the market significantly. Dietary supplement sales alone have quickly mushroomed into a multibillion dollar market in the United States.³⁴ Added to that would be the sales potential for tagatose as an excipient in drugs and cosmetics, and for recently determined GRAS uses in pharmaceutical products for canines and nonhuman primates. The true economic impact will become apparent only as the markets unfold.

Diet health benefits from the uses of tagatose as a drug for the diseases cited previously, as well as the indirect benefits discussed associated with its use in foods give this simple hexose sugar the potential for providing a healthier, more pleasurable life. To the extent, even if limited, that tagatose can replace sucrose, it may play an important role in permitting realization of the major benefits to health and longevity promised by dietary restriction.¹

Tagatose may turn out to be, as Spherix first termed it, "Nature's Best Sugar."

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