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December 9, 2005

RECEIVED
DEC 14 2005
OFFICE OF
FOOD ADDITIVE SAFETY

BY FEDEX

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

Re: Notification of GRAS Determination for L(+) Tartaric Acid Manufactured Using an Enzyme from Immobilized *Rhodococcus Ruber* Cells

To Whom It May Concern:

On behalf of S & G Resources, Inc. and Changmao Biochemical Engineering Co., we hereby submit this Notification to the Food and Drug Administration demonstrating that L(+) Tartaric Acid manufactured using an enzyme from immobilized *rhodococcus ruber* cells is generally recognized as safe (GRAS) for use in foods.

The submission consists of a GRAS notification, pursuant to proposed 21 C.F.R. §170.36 (62 Fed. Reg. 18960, April 17, 1997), as well as an expert statement from Michael Pariza, Ph.D. Three copies of these materials are enclosed.

Please note that we are waiting for the original signature from Changmao Biochemical Engineering Co. in China. As soon as that arrives, we will submit a fourth copy of the notification containing original signatures.

Please contact me directly with any questions.

Sincerely,

Diane McEnroe

Encls.

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GRAS Notification for L(+) Tartaric Acid Manufactured Using an Enzyme from Immobilized *Rhodococcus Ruber* Cells

Submitted By:
S & G Resources, Inc. and Changmao Biochemical Engineering Co.

December 9, 2005

I GRAS Exemption Claim

I-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)]

L-(+)-Tartaric acid manufactured using an enzyme from immobilized *Rhodococcus ruber* cells, hereafter referred to as tartaric acid, 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. The U.S. Food and Drug Administration (FDA) has previously affirmed that tartaric acid is GRAS (21 CFR §184.1099). The current product, which meets the Food Chemical Codex (FCC) specifications for tartaric acid, is manufactured using an enzyme from an immobilized non-pathogenic source and is chemically identical to that produced from crude cream of tartar, a byproduct of winemaking, which is the process described in the GRAS affirmation of tartaric acid. This product would be an alternative source of tartaric acid for existing food uses and thus would not result in any change in exposure. Therefore, the use of this tartaric acid in food as described below is exempt from the requirement of premarket approval.

Signed,

Michael Goldman
S & G Resources, Inc.

Date

06 Dec. 2005

Mr. Xinsheng Rui, President
Changmao Biochemical Engineering Co.

Date

I-B. Names and Addresses of Notifiers

Mr. Michael Goldman
S & G Resources, Inc.
266 Main Street
Medfield, MA 02052
USA

Mr. Xinsheng Rui, President
Changmao Biochemical Engineering Co.
West Chemical Area
Jiangbian Developing Zone
Changzhou, Jiangsu Province 213033
China

I GRAS Exemption Claim

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Signed,

Michael Goldman
S & G Resources, Inc.

Nov 29, 2005
Date

Mr. Xinsheng Rui, President
Changmao Biochemical Engineering Co.

Date

I-B. Names and Addresses of Notifiers

Mr. Michael Goldman
S & G Resources, Inc.
266 Main Street
Medfield, MA 02052
USA

Mr. Xinsheng Rui, President
Changmao Biochemical Engineering Co.
West Chemical Area
Jiangbian Developing Zone
Changzhou, Jiangsu Province 213033
China

I-C. Common Name of the Notified Substance

L-(+)-Tartaric Acid manufactured using an enzyme from immobilized *Rhodococcus ruber* cells.

I-D. Conditions of Intended Use in Food

This tartaric acid would be an alternative source of tartaric acid for use in food at levels not to exceed current good manufacturing practices. These uses may include use as a firming agent, as defined in 21 CFR §170.3(o)(10); a flavor enhancer as defined in 21 CFR §170.3(o)(11); a flavoring agent as defined in 21 CFR §170.3(o)(12); a humectant as defined in 21 CFR §170.3(o)(16); and a pH control agent as defined in 21 CFR §170.3(o)(23).

Initial specific intended uses may include use in wine to balance acid content, and in candies and beverages as an acidulent. It may also be used as an ingredient in the production of the esters diacetyl tartaric acid esters of mono-diglycerides (DATEM) and choline bitartrate.

The introduction of tartaric acid using an enzyme derived from immobilized *Rhodococcus ruber* cells will not result in any change in the overall exposure of the population to tartaric acid.

I-E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, tartaric acid manufactured using an enzyme from immobilized *Rhodococcus ruber* cells has been determined to be GRAS on the basis of scientific procedures (see Section IV).

I-F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the FDA upon request, or will be available for review and copying at reasonable times at the offices of:

Sidley Austin Brown & Wood LLP
787 Seventh Avenue
New York, NY 10019
Phone: 212-839-5615
Fax: 212-839-5599

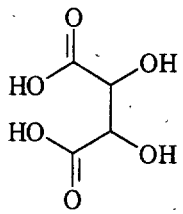
Should the FDA have any questions or additional information requests regarding this notification, **Emily Marden** or **Avital Malina** of Sidley Austin Brown & Wood LLP will supply these data and information.

II. Detailed Information About the Identity of the Substance

II-A. Identity

Changmao Biochemical Engineering Co. (hereafter referred to as Changmao) tartaric acid meets all current FCC specifications. The tartaric acid appears as colorless or translucent crystals, or as a white crystalline powder and is odorless with an acrid taste. Tartrates occur naturally in many foods including various fruits (*e.g.*, papayas, pineapples), dried coffee beans, and molasses. Exceptionally high concentrations of tartrates are present in wine with concentrations reported to range from 40 to 370 mg tartrates per 100 mL.

Structure:



Common or Usual Name:	L-(+)-Tartaric Acid
Chemical Name:	L-(+)-Tartaric Acid
Synonyms:	2,3-dihydroxy-butanedioic acid
Chemical Abstracts Service (CAS) Number:	87-69-4
Molecular weight:	150.085 g/mol
Empirical Formula:	$C_4H_6O_6$

II-B. Method of Manufacture

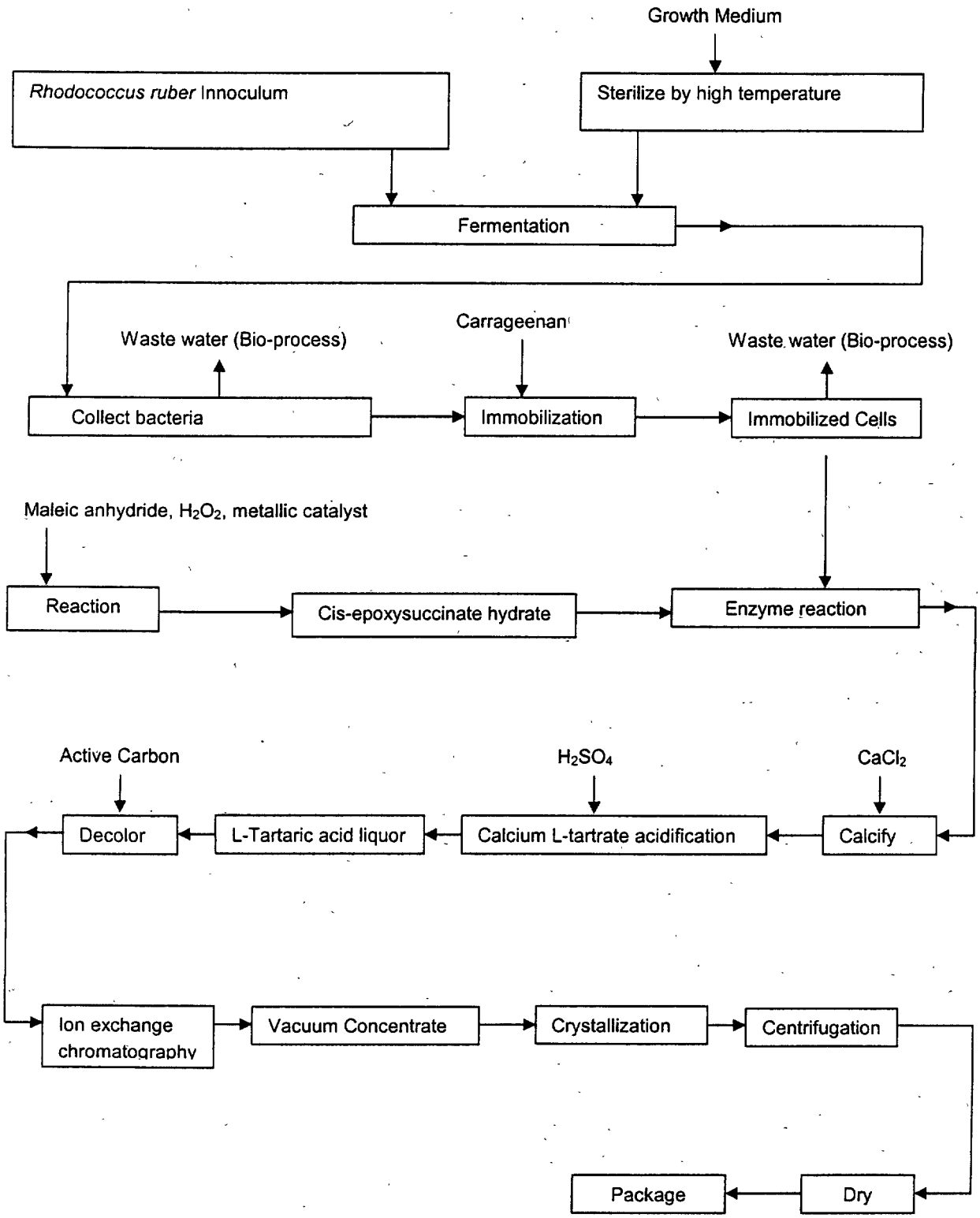
The tartaric acid manufactured by Changmao is produced by the conversion of maleic anhydride to tartaric acid through the enzymatic action of an enzyme, cis-epoxisuccinate hydrolase, contained in immobilized *Rhodococcus ruber* cells.

Following production of the *Rhodococcus ruber* cells by fermentation, the bacterial cells are immobilized through the addition of carrageenan. The substrate for the enzymatic reaction is produced separately by reaction of maleic anhydrate with hydrogen peroxide in the presence of a metallic catalyst. The product of the enzymatic reaction is calcified then separated and acidified to yield tartaric acid. Subsequently, the product undergoes several purification steps (decoloring, ion exchange chromatography) before being vacuum concentrated, crystallized, centrifuged, dried, and packaged.

All of the chemicals used in the manufacture of tartaric acid are of food grade quality with the exception of maleic anhydride for which there is no food grade material available. In order to ensure the quality of the product and to minimize carryover, additional safeguards were incorporated into the method. These safeguards included filtering out the catalyst and passing the solution through an ion exchange column to ensure there is no carryover. In addition, a heavy metals test is conducted with the final product to confirm the absence of the catalyst.

A schematic overview of the manufacturing process of tartaric acid manufactured using an enzyme from immobilized *Rhodococcus ruber* cells is provided in Figure 1.

Figure 1 Schematic Overview of the Manufacturing Process for L-(+)-Tartaric acid



II-C. Specifications for Food Grade Material

The chemical and physical specifications for tartaric acid are presented in Table 1. The analysis of 4 lots of tartaric acid demonstrated that the final product meets FCC specifications with regard to the chemical and physical specifications (FCC, 2003a).

Table 1 Physical and Chemical Specifications for L-(+)-Tartaric Acid Manufactured Using An Enzyme from Immobilized *Rhodococcus ruber*

Specification Parameter	FCC Requirements	Changmao Specifications
Assay	Not less than 99.7% and not more than 100.5% of $C_4H_6O_6$ after drying	99.7 to 100.5%
Lead (mg/kg)	Not more than 2	Not more than 2
Loss on Drying (%)	Not more than 0.5	Not more than 0.05
Optical (Specific) Rotation $[\alpha]^{25}D$	Between +12.0° and +13.0°	Between +12.0° and 13.0°
Oxalate	Passes test	Passes test
Residue on Ignition (%)	Not more than 0.05	Not more than 0.05
Sulfate	Passes test	Passes test
Arsenic (mg/kg)	Not more than 3	Not more than 3
D-(-)-Tartaric Acid (%)	NS	Not more than 0.30
Maleic Acid (%)*	Not more than 0.05	Not more than 0.05
Fumaric Acid (%)*	Not more than 1.0	Not more than 1.0

NS = not specified in the FCC
* meets FCC specification for malic acid (FCC, 2003b)

III. Self-Limiting Levels of Use

The level of use shall not exceed good manufacturing practices pursuant to 21 CFR § 184.1(b)(1).

IV. Basis for GRAS Determination

The determination that tartaric acid manufactured using an enzyme from immobilized *Rhodococcus ruber* cells is GRAS is on the basis of scientific procedures. The safety of tartaric acid is supported by numerous studies including acute, subchronic, chronic, and teratological toxicity studies in experimental animals, and mutagenicity assays. Tartaric acid has been previously evaluated by the FDA and affirmed as GRAS for uses specified in 21 CFR§ 184.1099.

IV-A. Safety of L-(+)-Tartaric Acid

The following comprehensive reviews and studies, which have been evaluated by the FDA in their assessment of tartaric acid, were conducted in support of the safety of tartaric acid and related compounds.

- Teratologic Evaluation of FDA 71-55, Tartaric Acid. Food and Drug Research Labs, Inc. (FDRL) Maspeth N.Y. 31 Jul 1973. PB223821.
- Scientific Literature Reviews on Generally Recognized As Safe (GRAS) Food Ingredients – Tartrates. Informatics, Inc, Rockville, MD. 1974. PB241955.
- Mutagenic Evaluation of Compound FDA 71-55, Tartaric Acid. Litton Bionetics, Inc., Kensington, MD. 13 Jan 1975. PB245445.
- Mutagenic Evaluation of Compound FDA 75-13, 000868-14-4, Potassium Acid Tartrate, FCC (Cream of Tartar) Powder. Litton Bionetics, Inc., Kensington, MD. 24 Dec 1975. PB254521.
- Evaluation of the Health Aspects of Potassium Acid Tartrate, Sodium Potassium Tartrate, Sodium Tartrate and Tartaric Acid as Food Ingredients. Federation of American Societies for Experimental Biology (FASEB), Bethesda, MD, Life Sciences Research Office (LSRO). 1979. PB301403.

Recent data support that only about 20% of orally administered tartaric acid is absorbed from the gastrointestinal tract in mammals (Martindale, 1989). The remaining 80% is fermented and used in the production of short chain fatty acids (SCFAs) by colonic microflora (Spiller *et al.*, 2003).

The acute oral LD_{50} of the sodium salt of tartaric acid is 4,360 mg/kg body weight in the mouse, and 5,290 mg/kg body weight in the rabbit, indicating a low order of toxicity (Locke *et al.*, 1942).

Several repeated dose oral toxicity studies have been conducted with tartaric acid or monosodium tartrate in rats, rabbits, and dogs. The results of these studies are summarized in Table 2.

Table 2	Summary of Repeated Dose Toxicity Studies with Tartaric Acid				
Species	Route/ Duration	Reported Dose	Calculated Dose of Tartaric Acid (mg/kg bw/day)[1]	Results	Reference
Sprague-Dawley Rat (10 males/group)	Oral gavage/ 7 days	2.57 g/kg bw/day monosodium L(+)-[^{14}C] or DL-[^{14}C] tartrate	2,010	Relative kidney weights were increased and evidence of crystalluria was observed	Down *et al.*, 1977
Wistar Rat (12 males)	Diet/ 16 weeks	100 mg/day	At least 400	Reduction in the incidence and growth of bladder and urinary calculi. Decrease in oxalic acid excretion.	Anasuya and Sasikala, 1989
Sprague-Dawley Rat (35/sex/group)	Diet/ 2 years	males: 0, 0.89, 1.62, 2.20, 3.10 g/kg bw/day; females: 0, 1.19, 2.05, 3.03, 4.10 g/kg bw/day of monosodium L(+) tartrate	males: 0, 710, 1,220, 1,840, 2,460; females: 0, 930, 1,600, 2,360, 3,200	Dose-related reduction in weight gain and food intake at doses ≥1,220 and 1,600 mg/kg bw/day in males and females, respectively. No other treatment related effects were observed. NOAEL: 3,200 mg/kg bw/day	Hunter *et al.*, 1977
Osbourne-Mendel Rat (12/sex/group)	Diet/ 2 years	0, 0.1, 0.5, 0.8, 1.2% tartaric acid in feed	0, 50, 250, 400, 600	No treatment-related effects were reported in any dose group. NOAEL 600 mg/kg bw/day	Fitzhugh and Nelson, 1947
New Zealand White Rabbit (15 males)	Diet/ 150 days	0, 7.7% tartaric acid in feed	0, 2,300	No adverse effects	Packman *et al.*, 1963
Dog (4, sex not specified)	Oral/ 90 to 114 days	990 mg/kg bw/day	990	Formation of urinary casts in 3 of 4 dogs, development of azotemia and subsequent death on day 90 in 1 of 4 dogs. Changes in body weight ranging from a gain of 30% to a loss of 32%.	Krop and Gold, 1945

NOAEL = no observed adverse effect level; bw = body weight

[1] Concentrations in feed were converted to mg/kg body weight/day doses using conversion factors from FDA (1993).

No increases in tumor incidences were reported in 2-year feeding studies in rats administered to 2,460 (males) or 3,200 (females) mg/kg body weight/day (Hunter *et al.*, 1977).

Negative results for tartaric acid were obtained, with and without metabolic activation, in the Ames assays using *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537, and in the *in vitro* chromosomal aberration assay in Chinese hamster fibroblast cell lines (Ishidate *et al.*, 1984). Tartaric acid was also negative in: (i) the host mediated assay in *Salmonella* strains TA-1530 and G-46, and in *Saccharomyces* strain D-3; (ii) the *in vitro* cytogenetic assay in human embryonic lung cultures; (iii) the *in vivo* cytogenetics assay in the

rat; and (iv) the *in vivo* dominant lethal assay in the rat (Litton Bionetics, Inc., 1975). These data support that tartaric acid lacks genotoxic potential.

The teratogenic potential of tartaric acid following oral administration was investigated in mice, rats, hamsters, and rabbits (FDRL, 1973). Rats and mice received doses of 181 and 274 mg/kg body weight/day, respectively, for 10 days, whereas hamsters received 225 mg/kg body weight/day for 5 days and rabbits received 215 mg/kg body weight/day for 13 days. No evidence of teratogenesis in soft or skeletal tissues was reported. In addition, no effects were observed on implantation, maternal survival rates, or fetal survival rates.

The results of the animal studies with tartaric acid support that it is of low oral toxicity, lacks carcinogenic and genotoxic potential, and is not teratogenic.

In addition to being affirmed GRAS by the FDA, tartaric acid has also been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JECFA evaluated fatty acid esters of glycerol with acetic, citric, lactic, and tartaric acids and established a group ADI of "not limited" on the provision that the total intake of tartaric acid does not exceed 30 mg/kg body weight/day in humans. This restriction was likely based on the ADI of 30 mg/kg body weight/day set by JECFA in 1974. However, since then, JECFA has concluded that the NOAEL of 1.2% (estimated by JECFA to be about 1,200 mg/kg body weight/day), the highest dose tested in a 2-year rat study (Fitzhugh and Nelson, 1947), provided sufficient margins of safety (>10,000 and >1,000) for the estimated levels of intake for tartaric acid (74 and 230 µg/kg body weight/day in Europe and the United States, respectively) (JECFA, 2000).

IV-B. Safety of Enzyme from *Rhodococcus Ruber*

Rhodococcus ruber was evaluated by Dr. Michael Pariza and found not to pose a toxicogenic or pathogenic concern. Thus, use of the enzyme isolated from *Rhodococcus ruber* cells is appropriate for the production of tartaric acid.

A letter from Dr. Pariza, detailing his findings, is appended to this notification.

V. References

Anasuya, A.; Sasikala, M. 1989. Tartaric acid inhibits urinary stone formation in rats. Nutr Res 9(5):575-580.

Down, W.H.; Sacharin, R.M.; Chasseaud, L.F.; Kirkpatrick, D.; Franklin, E.R. 1977. Renal and bone uptake of tartaric acid in rats: comparison of L(+) and DL-forms. Toxicology 8(3):333-346.

FASEB. 1979. Evaluation of the Health Aspects of Potassium Acid Tartrate, Sodium Potassium Tartrate, Sodium Tartrate and Tartaric Acid as Food Ingredients. Federation of American Societies for Experimental Biology (FASEB), Bethesda, MD, Life Sciences Research Office (LSRO). PB301403.

FCC. 2003a. Tartaric Acid. Food Chemicals Codex. Fifth Edition. Institute of Medicine of the National Academies, The National Academies Press, Washington, D.C. p. 467.

FCC. 2003b. Malic Acid. Food Chemicals Codex. Fifth Edition. Institute of Medicine of the National Academies, The National Academies Press, Washington, D.C. p. 266.

FDA. 1993. Appendix I. Table 14. Conversion table for test chemical treatment doses used in PAFA. In: Priority Based Assessment of Food Additives (PAFA) Database. Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition (CFSAN); Washington, DC, p. 58.

FDRL. 1973. Teratologic Evaluation of FDA 71-55 (Tartaric Acid). Food and Drug Research Labs, Inc. (FDRL) Maspeth N.Y. 31 Jul 1973. PB223821.

Fitzhugh, O.G.; Nelson, A.A. 1947. The comparative chronic toxicities of fumaric, tartaric, oxalic, and maleic acids. J Am Pharm Assoc Sci Ed 36:217-219.

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Ishidate, M. Jr.; Sofuni, T.; Yoshikawa, K.; Hayashi, M.; Nohmi, T.; Sawada, M.; Masuoka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22(8):623-636.

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Krop, S.; Gold, H.; Paterno, C.A. 1945. On the toxicity of hydroxyacetic acid after prolonged administration: Comparison with its sodium salt and citric and tartaric acids. J Am Pharm Assoc 24:86-89.

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Litton Bionetics, Inc. 1975b. Mutagenic Evaluation of Compound FDA 75-13. 000868-14-4, Potassium Acid Tartrate, FCC (Cream of Tartar), Powder Litton Bionetics, Inc., Kensington, MD. 24 Dec 1975. PB254521.

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Michael W. Pariza Consulting LLC
7102 Valhalla Trail
Madison, WI 53719

Michael W. Pariza, Member

November 21, 2005

Emily Marden
Sidley Austin Brown & Wood LLP
787 Seventh Avenue
New York, NY 10019

Dear Ms. Marden,

I am writing in regard to your request for a safety evaluation of the cis-epoxysuccinate hydrolase from *Rhodococcus ruber* that is used in the manufacture of tartaric acid by the Changmao Biochemical Engineering Company. My opinion is based on consideration of the documents and materials provided by the Changmao Biochemical Engineering Company, S&G Resources, Inc., and other relevant sources including the safety evaluation decision tree described in the publication, MW Pariza and EA Johnson; 2001; Evaluating the safety of microbial enzyme preparations used in food processing: Update for a new century; *Regulat. Toxicol. and Pharmacol.* 33:173-186.

The production organism for the cis-epoxysuccinate hydrolase enzyme was identified as *Rhodococcus ruber* by Accugenix, one of the world's leading companies specializing in the identification of microorganisms. A detailed literature search using Google Scholar, EBSCOhost, PubMed, HeinOnline, and the National Library of Medicine's IndexCat was conducted. Several hundred publications relating to *Rhodococcus ruber* were identified in the peer-reviewed scientific literature, none of which indicated that this organism has been associated with human illness. Hence it is reasonable to conclude that *Rhodococcus ruber* is both nonpathogenic and nontoxigenic. The enzyme immobilization process described in the manufacturing procedure is appropriate for the manufacture of food ingredients.

Based on these considerations, I conclude that the cis-epoxysuccinate hydrolase from *Rhodococcus ruber* described by the Changmao Biochemical Engineering Company is safe and suitable for the manufacture of food grade tartaric acid.

Sincerely,

Michael W. Pariza
Wisconsin Distinguished Professor of
Food Microbiology and Toxicology
Member, Michael W. Pariza Consulting LLC

SUBMISSION END