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July 22, 2008

Robert L. Martin, Ph.D.
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: GRAS Notice for gamma-amino butyric acid (GABA)

Dear Dr. Martin:

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the *Federal Register* [62 FR 18938 (17 April 1997)], I am submitting in triplicate, as the notifier [Pharma Foods International Co., Ltd., 1-49 Goryo-Ohara, Nishikyo-ku, Kyoto, 615-8245, Japan], a Notice of the determination, on the basis of scientific procedures, that *gamma*-amino butyric acid (GABA) derived from L-glutamate *via Lactobacillus hilgardii* fermentation, produced by Pharma Foods International (PFI), as defined in the enclosed documents, is GRAS under specific conditions of use as a food ingredient, and therefore, is exempt from the premarket approval requirements of the *Federal, Food, Drug and Cosmetic Act*. Information setting forth the basis for the GRAS determination, which includes a comprehensive summary of the data available and reviewed by an independent panel of experts (the Expert Panel) in support of the safety of PFI's GABA ingredient under the intended conditions of use, as well as *curricula vitae* evidencing the qualifications of the members of the Expert Panel for evaluating the safety of food ingredients, also is enclosed for review by the agency.

I trust that the enclosed Notice is acceptable. Should you have any questions or concerns regarding this GRAS Notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner.

Sincerely,

Yoshiaki Yoshikuni Ph.D
General Manager
Research and Planning Dept.
Pharma Foods International Co., Ltd.
1-49 Goryo-Ohara, Nishikyo-Ku,
Kyoto, 615-8245
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y-yoshikuni@pharmafoods.co.jp

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I GRAS Exemption Claim

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

As defined herein, *gamma*-amino butyric acid (GABA) derived from L-glutamate, has been determined by Pharma Foods International Co., Ltd. (PFI) to be Generally Recognized as Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of intended use in food. Therefore, the use of PFI's GABA as a food ingredient as described below is exempt from the requirement of premarket approval.

Signed,

July 22, 2008
Date

Yoshiaki Yoshikuni Ph.D.
General Manager
Research and Planning Dept.
Pharma Foods International Co., Ltd.

B. Name and Address of Notifier

Yoshiaki Yoshikuni Ph.D
General Manager
Research and Planning Dept.
Pharma Foods International Co., Ltd.
1-49 Goryo-Ohara, Nishikyo-Ku,
Kyoto, 615-8245
Japan
y-yoshikuni@pharmafoods.co.jp

C. Common Name of the Notified Substance

Gamma-amino butyric acid (GABA)

D. Conditions of Intended Use in Food

PFI intends to market GABA, derived from glutamic acid *via* a *Lactobacillus hilgardii* fermentation process, as a food ingredient in the United States in a variety of food products including beverages and beverage bases, chewing gum, ready-to-drink coffee and tea products, and candy at concentrations ranging from 0.04 to 4% in various food types. GABA is not intended for use in meat or meat-containing products.

E. Basis for the GRAS Determination

Pursuant to 21 CFR §170.30, GABA has been determined by PFI to be GRAS on the basis of scientific procedures (U.S. FDA, 2008). This GRAS determination is based on data generally available in the public domain pertaining to the safety of GABA for use in food, as discussed herein and in the accompanying documents, and on a consensus among a panel of experts[1] who are qualified by scientific training and experience to evaluate the safety of GABA as a component of food [see Appendix A, **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GABA FOR USE AS A FOOD INGREDIENT**[2]].

F. Availability of Information

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

Pharma Foods International Co., Ltd.
1-49 Goryo-Ohara, Nishikyo-ku
Kyoto, 615-8245
Japan

Should the FDA have any questions or additional information requests regarding this Notice, PFI also will supply these data and information.

II. Detailed Information Regarding the Identity of the Substance

A. Identity

The common or usual name of this product is GABA. PFI's GABA ingredient (GABA) is a spray-dried white to light yellow crystalline powder produced *via* a *L. hilgardii* catalyzed fermentation process. The ingredient contains at least 80% GABA, with the remaining material characterized primarily by glutamate and trace amounts of other free amino acids, carbohydrates, and lipids, which are carry-over products of fermentation.

Common or Usual Name:	GABA
Chemical Name:	*gamma*-amino butyric acid
Chemical Abstracts Service (CAS) Number:	56-12-2

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[1] The Panel of Experts consisted of Prof. Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University, School of Medicine), Prof. William J. Waddell, M.D. (University of Louisville School of Medicine) and Prof. Stephen L. Taylor, Ph.D. (University of Nebraska).

[2] Note that PFI's GABA ingredient - the ingredient that is the subject of this notification - is referred to as PHARMAGABA throughout the Expert Panel Statement in Appendix A. This simply refers to a potential trade name for the ingredient, highlighting that the ingredient is a product of "Pharma" foods.

Empirical Formula: $C_4H_9NO_2$
Molecular Weight: 103.12

Structural Formula: See Figure 1.0

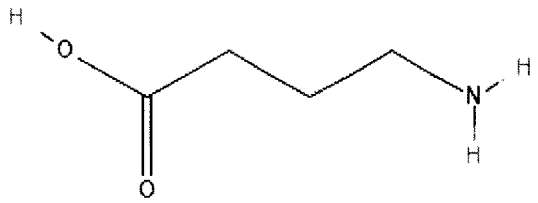

Figure 1.0 Structure of GABA

B. Method of Manufacture

A pre-fermentation broth is prepared by dissolving monosodium glutamate, glutamic acid, yeast extract, glucose, and glycerin fatty acid ester in water inside a sealed fermentation vessel. The mixture is then sterilized using a temperature of 121°C for a period of 20 minutes. Following sterilization, the mixture is cooled and the vessel pressure reduced. Under these conditions, the fermentation broth is stirred for several hours. Once complete, the *Lactobacillus* strain, *L. hilgardii* K-3, is then added to the media and fermentation takes place over a few days. Once fermentation is complete the mixture is sterilized by appertization at 97°C for 30 minutes. Once cool the solution then undergoes a vacuum concentration step followed by the addition of activated charcoal to the vessel. After brief mixing, the bacteria and large particulates are removed from the solution by filter pressing with a diatomaceous earth/cellulose filter. The solution is then filter sterilized using a 0.65 µm filter. The filtered solution is vacuum concentrated a second time and filtered once again through a 20.0 µm filter. The solution is stored in polyethylene/nylon bags for transport to the spray-drying tower. After spray drying, iron particulates are removed by two consecutive steps with magnetic bars. The final dried product is >80% GABA, and the GABA powder is then sifted through a #42 mesh before storage in aluminum pouches. A schematic diagram of the manufacturing process for GABA is provided in Figure 2.0 All processing aids used the manufacture of GABA are used in compliance with appropriate federal regulations (see Table 1.0).

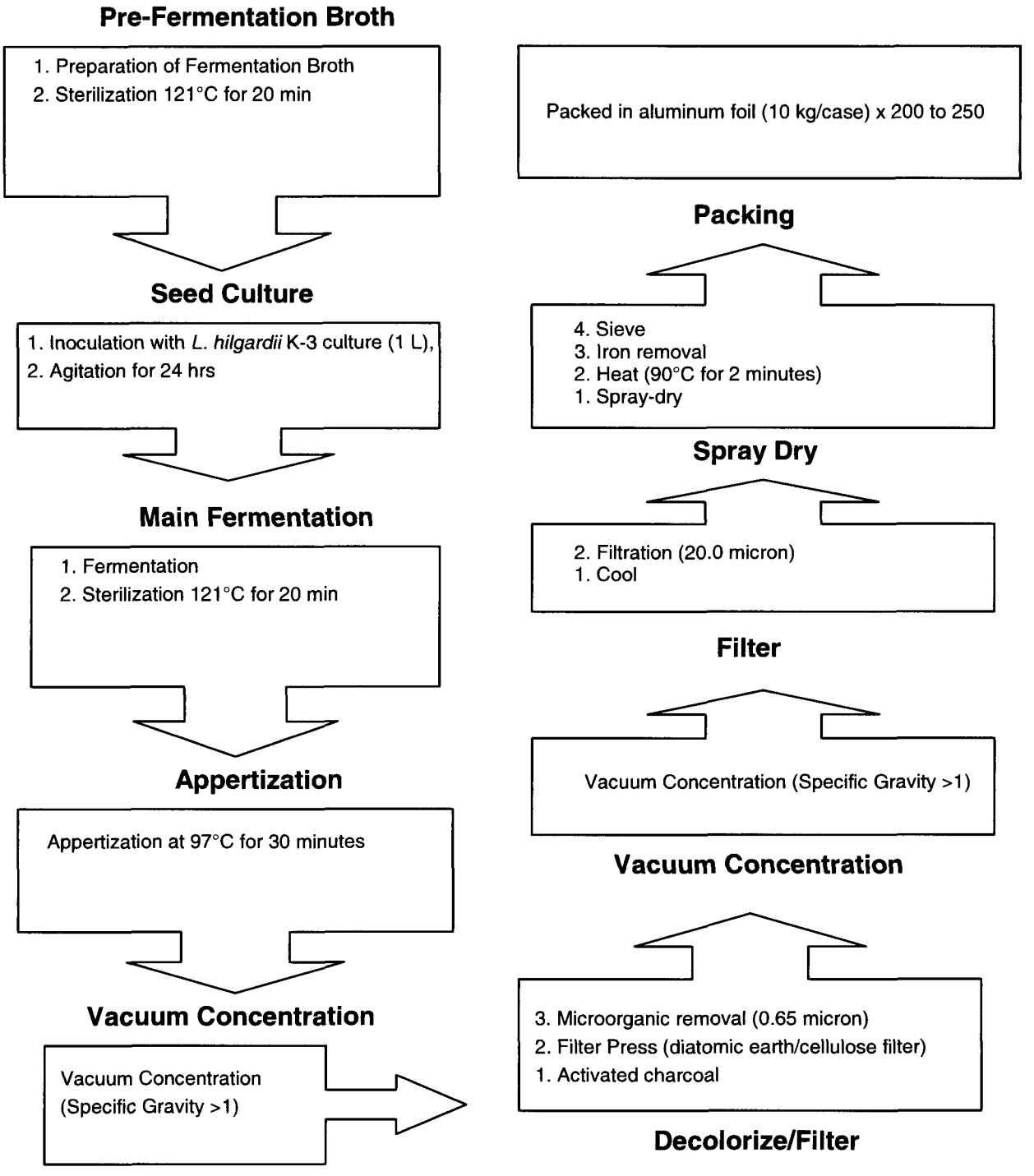

Figure 2.0 Schematic Overview of the Manufacturing Process for GABA

Table 1.0 List of Processing Aids Used in the Manufacture of GABA	
Processing Aids used in Manufacture of GABA	**Code of Federal Regulation Citation or GRAS Number**
Glycerine fatty acid[1] ester (emulsifier)	21 C.F.R. §172.854 Polyglycerol esters of fatty acids.
Activated Carbon	21 C.F.R. §177.1210 Closures with sealing gaskets for food containers.
Diatomaceous earth/cellulose filter • Cellulose • Natural diatomaceous earths • Perlite • Polypropylene gaskets • <3% polyolefine fibers	Diatomaceous earth and perlite products used to make filtration media are GRAS for use as filter aids in food processing (U.S. FDA, 2002). 21 CFR § 177.1520 Olefin polymers. 21 CFR § 175.300 Resinous and polymeric coatings.
0.65 µM filter (Polysulphone type)	21 CFR § 177.2910 Ultra-filtration membranes. 21 CFR § 177.1655 Polysulfone resins.
0.20 µM filter (Polyether type)	21 CFR §177.2910 Ultra-filtration membranes. 21 CFR § 177.2260 Filters, resin-bonded.

[1]Fatty acid source = Palm oil

C. Specifications and Analytical Data

In order to ensure that a consistent product is produced, PFI has established specifications for the final ingredient (see Table 2.0). Representative lots are routinely assayed to ensure compliance with final product chemical, physical, and microbiological specifications. A copy of the specifications and batch analyses results for 3 non-consecutive lots of GABA is provided in Appendix B (Table B-1). Certificates of analyses also are included (Appendix B; Attachment B-1). The ingredient comprises GABA at a minimum purity of 80%, with the remaining material composed primarily of glutamate, small amounts of free amino acids, ash, and moisture which accounts for the remainder of the final product (see Appendix B, Table B-2). Trace amounts of carbohydrate (<1%) and lipid (<0.1%) also can be detected in GABA. Specifications for heavy metal and microbial contamination were determined to be acceptable for use as a food ingredient. Batch analysis confirms that ash is limited to levels below 10%, and 90% of the total ash content was accounted for by sodium chloride; no minerals at levels of toxicologic concern were noted, and iron levels were low at 0.15 milligrams (mg)/100 grams (g) GABA (see Appendix B, Table B-2). The ingredient typically contains a variety of free amino acids and dipeptides, which originate from the fermentation medium. High performance liquid chromatography (HPLC) analysis of the total acid-hydrolyzed amino acid content of GABA corresponded on a weight-to-weight basis to the total free amino acid and dipeptide content of the ingredient (pre-acid hydrolysis), indicating that the product is free of contaminating proteins (See Appendix B; Table B-3). Unmetabolized glutamate remaining from the fermentation process accounted for the majority of the amino acid content of the final product. In addition to contamination by aerobic bacteria and yeast and mold, which are limited by quality control procedures and have specifications of <1,000 CFU and <300 CFU respectively, the transfer of *L. hilgardii* into the final product is prevented by the inclusion of a filter sterilization (0.65 micron filter) step in the manufacturing process. Moreover, lactic acid bacteria such as *L. hilgardii* are

highly sensitive to oxidative environments, and it is unlikely that the organism would survive the oxidative conditions of spray drying, further ensuring that microbial contamination of *L. hilgardii* in the final product is prevented. Analysis of the final product confirmed the absence of *L. hilgardii* K-3. Finally, although it is not expected that the fermentation conditions would be conducive to contamination of the final product with *L. hilgardii* K-3-derived biogenic amines or ethyl carbamate (see Section IV-G), HPLC analysis of GABA was conducted and confirmed the absence of histamine and ethyl carbamate in the ingredient (see Appendix B; Attachments B-3 and B-4).

Table 2.0 Product Specifications for GABA

Specification Parameter	Specification[1]	Method of Analysis
Appearance	White to light-yellow powder	Visual
gamma-Aminobutyric acid (GABA)	>80%	HPLC, based on Bianchi *et al.*, 1999
Moisture (Loss on drying)	<5%	105°C, 5 hours, based on JSSFA, 2000, p. 29
Ash	<10%	550 to 600°C, 5 hours, without sulfuric acid, based on JSSFA, 2000, p. 7
Lead[2]	<0.5 ppm	Atomic Absorption Spectroscopy
Arsenic	<2 ppm	DDTC-Ag Luminosity absorbance, based on JSSFA, 2000, p. 25
Total Aerobic Counts	<1,000 CFU/g	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35
Yeast and Mold	<300 CFU/g	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35.
Coliform/*Escherichia coli*	Negative	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35.

CFU = colony-forming units; DDTC-Ag = silver diethyldithiocarbamate; HPLC = high-performance liquid chromatography; JSSFA, 2000 = Japan's Specifications and Standards for Food Additives (7th ed.)
[1] Product is characterized to a purity of 95%, the remaining 5% of the ingredient is comprised of free amino acids (mainly glutamate), and small quantities of carbohydrates and lipids (see Appendix B, Table B-2).
[2] See Attachment B-2 of Appendix B for certificates of analyses pertaining to lead analysis

PFI's GABA meets appropriate food-grade specifications. Bulk stability studies indicate that GABA is stable for up to 27 months when stored at room temperature (see Appendix C). GABA also was determined to be stable in solution at a concentration of 5% over a broad pH range (2 to 7) and under elevated temperatures (100°C) (Appendix C; Figures C-1 to C-3). The results of the stability studies indicate that GABA is expected to be stable for use under the proposed food uses.

III. Self-Limiting Levels of Use

The levels of use of GABA are limited due to food formulation issues, as the ingredient is expected to impart an undesirable flavor to the food when incorporated at high concentrations. Specific thresholds for these effects have not been determined.

IV. Basis for GRAS Determination

The determination that GABA is GRAS is on the basis of scientific procedures, and the information supporting the general recognition of the safe use of GABA includes:

- Data pertaining to the identity, intended use, and estimated intake of GABA
- Background occurrence of GABA as a natural or added (Japan) component of various foods consumed in the U.S and Japan, including estimates of background exposures in these countries.
- Information characterizing the kinetics and metabolic fate of GABA, including information studying the capacity of GABA to cross the blood-brain-barrier from the systemic circulation.
- The entirety of animal and human studies assessing the safety of GABA consumption.
- Data pertaining to the safety of *L. hilgardii* for use in the production of a food ingredient.

Moreover, these data were reviewed by a Panel of Experts, qualified by scientific training and experience to evaluate the safety of GABA as a component of food, who concluded that the proposed uses of GABA are safe and suitable and would be GRAS based on scientific procedures [see Appendix A – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GABA FOR USE AS A FOOD INGREDIENT]**. A summary of the data is presented herein.

A. Estimated Intake of GABA

PFI intends to market GABA as a food ingredient in the United States in a variety of food products including beverages and beverage bases, chewing gum, ready-to-drink coffee and tea products, and candy, at use levels of 0.04 to 4% GABA per serving (30 to 200 mg GABA/serving). The individual proposed food uses and use levels for GABA are summarized in Table 3.0. Food codes representative of each proposed food use were chosen from the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Survey (NHANES) (CDC, 2006; USDA, 2008) and were grouped in food use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (U.S. FDA, 2008).

Table 3.0 Summary of the Individual Proposed Food Uses and Use Levels for GABA in the U.S.

Food Category	Proposed Food Uses	GABA Level (mg/serving)	Serving Size (g or mL)	Use Levels of GABA (%)
Beverages and Beverage Bases	Energy, Sport, and Isotonic Drinks	30 to 200	500	0.04 to 0.048
	Meal Replacement Drinks	30 to 100	100	0.1 to 0.12
Chewing Gum	Chewing Gum	10 to 100	3	3.33 to 3.996
Coffee and Tea	Coffee, Ready-to-Drink	Up to 100	240*	0.042 to 0.050
	Tea, Ready-to-Drink	Up to 100	240*	0.042 to 0.050
Hard Candy	Hard Candy (Including Mints)	30 to 70	30	0.23 to 0.276
Soft Candy	Chocolate Confections	30 to 100	100	0.1 to 0.12

*RACC = Reference Amounts Customarily Consumed per Eating Occasion as per 21 CFR §101.12 (U.S. FDA, 2008).

During the intake calculations it was assumed that GABA was 100% pure GABA. Although this assumption would result in a slight overestimation of intakes, it was performed for ease of comparison to available safety data. Approximately 37.2% of the total U.S. population was identified as consumers of GABA from the proposed food uses (3,073 actual users identified). Consumption of GABA-containing foods by the total U.S. population would result in estimated mean all-person and all-user intakes of GABA of 47.03 mg/person/day (0.73 mg/kg body weight/day) and 126.30 mg/person/day (1.97 mg/kg body weight/day), respectively (Tables 4.0 and 5.0). The 90th percentile all-person and all-user intakes of GABA by the total population from all proposed food uses of GABA were estimated to be 150.19 mg/person/day (2.40 mg/kg body weight/day) and 266.40 mg/person/ day (4.22 mg/kg body weight/day), respectively.

Table 4.0 Summary of the Estimated Daily Intake of GABA from All Proposed Food Uses of GABA in the U.S. by Population Group (2003-2004 NHANES Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-User Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infants	0 to 2	16.5	153	9.46	17.48	55.86	177.10
Children	3 to 11	36.1	465	28.91	96.00	72.91	144.00
Female Teenagers	12 to 19	40.1	398	37.59	139.86	108.75	215.34
Male Teenagers	12 to 19	38.2	382	65.19	186.90	148.58	294.00
Female Adults	20 and Up	40.9	871	48.27	159.58	127.46	256.58
Male Adults	20 and Up	41.7	804	55.48	192.00	147.82	349.87
Total Population	All Ages	37.2	3,073	47.03	150.19	126.30	266.40

At 41.7%, male adults were identified as the greatest percentage of users of the population groups, followed by female adults at 40.9% and female teenagers at 40.1%, while infants were

identified as the lowest percentage of users of any population group at 16.5%. When mean consumers were assessed, the greatest mean all-person and all-user intakes of GABA on an absolute basis were male teenagers, at 65.19 and 148.58 mg/person/day, respectively (corresponding to 1.04 and 2.37 mg/kg body weight/day). On a body weight basis, the mean all-person intake of GABA was estimated to be highest in male teenagers (1.04 mg/kg body weight/day), while the mean all-user intake was highest in infants (4.59 mg/kg body weight/day).

When heavy consumers (90th percentile) were assessed, all-person and all-user intakes of GABA from all proposed food uses of GABA were determined to be greatest in male adults (192.0 and 349.87 mg/person/day, respectively).

Table 5.0 Summary of the Estimated Daily per Kilogram Body Weight Intake of GABA from All Proposed Food Uses of GABA in the U.S. by Population Group (2003-2004 NHANES Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-User Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infants	0 to 2	16.5	153	0.78	1.56	4.59	14.89
Children	3 to 11	36.1	465	0.98	3.21	2.48	5.83
Female Teenagers	12 to 19	40.1	398	0.64	2.44	1.85	3.54
Male Teenagers	12 to 19	38.2	382	1.04	3.03	2.37	5.19
Female Adults	20 and Up	40.9	871	0.69	2.20	1.81	3.83
Male Adults	20 and Up	41.7	804	0.66	2.15	1.75	3.85
Total Population	All Ages	37.2	3,073	0.73	2.40	1.97	4.22

On a body weight basis, children and infants were identified to have the greatest all-person and all-user 90th percentile intakes of GABA, respectively, with values of 3.21 and 14.89 mg/kg body weight/day, respectively (Table 5.0). It should be noted, however, that the specified GABA food uses are not intended to be marketed to infants and children; thus, the actual infant and child consumption of GABA is expected to be highly limited, and although an estimate of the consumption of GABA on a body weight basis in infants and children from all proposed food uses has been included for completeness of this report, it is considered to be a gross over-estimate of the actual expected intake of GABA by infants and children from its addition to food. This is supported by the fact that the lowest percentage of users, as well as the lowest intakes on an absolute basis, were determined to be in children and infants.

Background Dietary Consumption of GABA

GABA exists naturally in many different foods at low levels, and in higher levels in fermented food products. Examples of GABA-rich foods include tomatoes, potatoes, melons, and the

traditional Korean and Japanese food, kimchi. These foods have been reported to contain from 27.5 to 74.5 mg GABA/100 g food product, and green tea leaves have been reported to contain as much as 100 to 200 mg of GABA/100 g on a wt/wt basis (Hayakawa *et al.,* 1997; Matumoto *et al.*, 1997; Akastu, 2000). In addition, other foods are likely to contain appreciable amounts of GABA as a result of the processing methods used to obtain them (*e.g.*, lactic acid-fermented foods, such as cured meats and cheeses).

Using annual *per capita* consumption data and published information on the GABA content of various foods, the average U.S. intake of GABA from its natural occurrence was estimated to be 135.56 mg/person/day (Stofberg and Grundschober, 1987; Hayakawa *et al.,* 1997). Estimations of GABA exposure from the consumption of GABA naturally occurring in the diet also were performed using Japanese survey data (Japan National Health and Nutrition Examination Survey 2005) where intakes were estimated to be 80.20 mg/person/day. Therefore, background exposure to GABA from a typical North American diet is expected, and the intake of GABA under the conditions of intended use is comparable to typical dietary exposure from GABA-containing foods.

Many GABA-enriched foods have been launched onto the Japanese market over the past 20 years with positive consumer reception. Products that currently are enriched with GABA in Japan include tea, germinated rice products, pickles, fermented milk, and chocolate. The GABA content of these products range from approximately 10 mg/100 g in germinated rice to 280 mg/50 g in chocolate. Moreover, GABA was identified as a dietary ingredient in a number of dietary supplement products currently available on the U.S. market at levels ranging from 100 to 750 mg/capsule or tablet, and recommended intakes of 750 mg GABA/person/day. The consumption of up to 1,500 to 5,000 mg of GABA/day has been indicated for some products, without recommended durations for use.

B. Metabolic Fate and Kinetics

As PFI's GABA ingredient comprises >80% GABA, data pertaining to the expected metabolic fate and kinetics of this compound were reviewed in order to assess the absorption, distribution, metabolism and excretion of GABA under the intended conditions of use in foods and beverages.

There is limited information detailing the absorption and kinetic properties of orally administered GABA. Evidence of specific GABA transporters in the rat jejunum has been reported (Nácher *et al.*, 1994); however, the maximum plasma levels of GABA following oral administration of GABA in rats were 20-fold less than those observed following intraperitoneal administration of the same dose, suggesting that absorption and/or bioavailability in rodents (and probably humans) is low (van Gelder and Elliott, 1958). The kinetics of GABA were demonstrated to be similar among rats, rabbits, and cats, with rapid clearance rates and half-lives of approximately 20 minutes (van Gelder and Elliott, 1958). The tissue distribution of radiolabeled GABA following

systemic administration was similar in the rat and mouse, where GABA was distributed primarily to the liver, kidneys, and muscle. In the mouse, significant GABA levels also were detected in the urinary bladder, gastrointestinal wall, pituitary gland, and cartilage of the spine, ribs, and trachea; however, the GABA radioactivity rapidly diminished post-injection (van Gelder and Elliott, 1958; Hespe *et al.*, 1969). It should be noted, however, that the methodology used to measure GABA radioactivity in these studies was non-qualitative, and information distinguishing radioactivity derived from GABA *versus* metabolites of GABA, or potential bacterial degradation products could not be determined. No evidence of GABA bioaccumulation or organ-specific retention was observed in any of the reviewed studies[3]. No information detailing the absorption and kinetics of GABA consumption in humans was identified in the published literature.

GABA is an endogenous compound, and given its importance as a neurotransmitter, metabolism of the molecule has been well characterized in humans and animals. The liver is considered to be the primary metabolic site of extra-cerebral GABA, and rats display a large capacity for GABA uptake by this organ. For example, *ex vivo* liver perfusion concentrations had to be increased 60-fold above baseline plasma levels (84 ng/mL) before saturation of GABA uptake occurred in rats (Schafer *et al.*, 1981; Ferenci *et al.*, 1988). The catabolism of GABA occurs exclusively *via* GABA transaminase where the compound is used as a carbon source in the tricarboxylic acid cycle (TCA), resulting in carbon dioxide (CO_2) as the primary waste product (Ferenci *et al.*, 1988); thus, GABA is essentially utilized as an energy source by the body, and is metabolized to innocuous compounds.

Based on an extensive body of evidence, the ability of the blood-brain barrier (BBB) to prevent GABA permeation from the plasma to the brain, although not absolute, is substantial and not significantly affected by exogenously administered GABA (van Gelder and Elliott, 1958; Hespe *et al.*, 1969; Kuriyama and Sze, 1971; Oldendorf, 1971; Frey and Löscher, 1980; Krantis, 1984; Al-Sarraf, 2002; Al-Awadi *et al.*, 2006). For example, in the rat, a 1,250-fold increase in the dose of GABA administered intraperitoneally resulted in an increase in the levels of GABA in the cerebrospinal fluid (CSF) of only 30-fold. The poor dose-response relationship between the administered dose and GABA permeation across the BBB also was observed in radiokinetic studies, where increases in plasma concentrations of GABA displayed little effect on the overall permeation rates of GABA across the BBB of rats (Krantis, 1984). Even under experimental conditions where GABA permeation rates were increased between 3- to 16-fold [*e.g.*, in young rodents or in Spontaneously Hypertensive Rats], the increased permeation rate was not reflected in increased GABA in the central nervous system (Al-Sarraf, 2002; Al-Awadi *et al.*, 2006). These observations may be explained by studies conducted by Kakee *et al.* (2001) that showed that the efflux rate of GABA though the BBB of rats exceeded influx by approximately 16-fold, and studies indicating that GABA transaminase can rapidly degrade even large doses

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[3] Retention of radioactivity in the Harder's glands was noted during autoradiography studies by Hespe *et al.* (1969); however, this organ is not relevant to humans.

of intra-cerebrally administered GABA (Kuriyama and Sze, 1971). Slight species differences in BBB permeability of GABA were suggested by van Gelder and Elliott (1958) where GABA entry into the brain may be even more restricted in higher order mammals. In contrast to rodents, where small amounts of GABA have been shown to enter the brain, van Gelder and Elliott (1958) reported that the levels of GABA in the CSF were undetectable 30 minutes following the intravenous administration of high doses of GABA (200 mg/kg body weight) to monkeys.

C. Studies in Animals

Acute Toxicity Studies

A single-dose, oral toxicity study was conducted by Japan Food Research Laboratories (JFRL, 2002) in 4-week-old male and female Wistar rats (10/sex/group) using a study design based on the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals (OECD Guideline 401) (OECD, 1987). The test article used in the study was GABA-20 (GABA-20), which was PFI's GABA ingredient (≥80% pure GABA) diluted 4-fold (with dextrose), and therefore had a purity of at least 20% GABA. Animals received a single gavage of GABA-20 dissolved in water to provide a dose of 5,000 mg/kg body weight of GABA-20, which would correspond to an acute GABA exposure of 1,000 mg/kg body weight. A control group received equal volumes of water. Standard clinical monitoring and observations of mortality were recorded over a 14-day period. No differences in body weights were observed on Days 7 and 14 for both male and female test animals relative to controls. No evidence of morbidity or incident of mortality was reported, and hence the LD_{50} of GABA-20 in mice was >5,000 mg/kg body weight (or approximately >1,000 mg GABA/kg body weight). Oral LD_{50} values as high as 12 g GABA/kg body weight have been reported in mice (Oshima *et al.*, 1965).

Kato *et al.* (2005) conducted a single-dose toxicity study of a GABA-containing fermented milk in 5-week-old CRj:DC(ICR) mice that were randomized to 1 of 3 treatment groups (number of animals per group not indicated) receiving gavage doses of unfermented milk (skim milk), fermented milk containing 10 mg GABA/100 mL (DGB10), or fermented milk containing 25 mg GABA/100 mL (DGB25). The GABA-containing milk was prepared by fermenting skim milk with *Lactobacillus casei* and *Lactococcus lactis*, and the final product was then formulated with added maltitol, pectin, and soy polysaccharide. Oral gavage volumes were 20 mL fluid/kg body weight for each treatment group, such that mice allocated to treatment groups DGB10 and DBG25 received 2 and 5 mg/kg body weight of GABA respectively. Standard endpoints of behavior and growth were monitored over a 14-day period without evidence of toxicity or changes in body weights among the groups.

Subchronic Toxicity Studies

A 28-day toxicity study was conducted by the Japan Scientific Food Association in male and female Wistar rats (Hayami *et al.,* 2005). The test article used in the study was GABA-20, which

as described, was PFI's GABA ingredient diluted to 20% purity, and identical to the GABA source used in the acute toxicity study of JFRL (2002). Rats (32 days of age) were randomized to 1 of 2 groups (20/sex/group) receiving standard rat chow (control) or feed supplemented with 1% GABA-20 [providing approximately 1,000 mg GABA-20/kg body weight/day (U.S. FDA, 1993), which would correspond to approximately 200 mg GABA/kg body weight/day]. Standard clinical monitoring, body weight gain, and food consumption were recorded throughout the course of the experiment. On Day 28, hematological and biochemical tests were performed and standard gross pathology and measurement of organ weights also were conducted. Histopathological testing was performed for brain, heart, liver, kidney, testes, and ovaries. Over the course of the study, no significant differences in weight gain were reported between the treated and control groups, and no differences in average food consumption were observed. No signs of morbidity were observed and no mortality was reported. There were no changes in hematology or biochemical parameters for either male or female treated animals relative to controls; however, it should be noted that a number of biochemical parameters were below the detection limit of the analytical technique in both control and treatment groups, including alanine aminotransferase (ALT)[4], lactate dehydrogenase (LDH), bilirubin, and cholesterol, indicating potential limitations to the analytical sensitivity and methodology. There were no abnormal findings noted during necropsy The only significant difference in organ weights was absolute and relative testis weights, which were increased from control by 7 and 6% ($p<0.05$), respectively; however, this increase was reported by the authors to be within the range of historical control data. Histopathological investigations also were unremarkable.

Kato *et al.* (2005) conducted a 28-day study in male and female Crj:CD(SD) rats. Following a 1-week acclimatization period, male rats weighing 179.9 to 195.4 g and female rats weighing 145.5 to 163.1 g were randomized to 1 of 3 groups (4 animals/sex/group). The animals were administered, by oral gavage, unfermented milk (skim milk, control), DGB10, or DGB25, which were prepared as per their acute study, with the rats allocated to the DGB10 and DBG25 treatment groups receiving 2 and 5 mg GABA/kg body weight, respectively. The animals were housed under standard animal care conditions, and were permitted *ad libitum* access to feed and water. Rats were observed for signs of toxicity on a daily basis and feed intake, water consumption, and body weights were evaluated once a week. Routine clinical chemistry, hematology, and urinalysis were performed. At the end of the study period, the animals were necropsied, selected organs were weighed, and tissues were preserved for histopathological examination. No significant differences in body weight gain were observed between groups. Other than a slight decrease (<10%; $p<0.05$) in food intake in DGB25 females on Day 11 and decreased (<10%; $p<0.05$) water intake for DGB10 females on Day 4, no significant differences in food or water intakes were noted. With the exception of a slight (2.4%; $p<0.01$) increase in urine specific gravity in DGB25 males, quantitative and qualitative urinalysis was unremarkable among groups. The change observed in urine specific gravity was modest, did not correlate

[4] Also commonly referred to as glutamate pyruvate transaminase (GPT).

with changes in urine protein or glucose, and was not observed in females, and therefore was considered a spurious finding by the authors. A few sporadic significant changes in hematological parameters (*i.e.*, prothrombin time, mean corpuscular hemoglobin concentration, hematocrit, basophil number, and percent basophil) were noted; however, the changes were modest (<10% for all parameters except basophil number, which decreased from 0.01 to 0.00), in many cases were not dose responsive, and in all cases did not occur in both sexes. Therefore, the various changes were not considered toxicologically relevant. There were no toxicologically relevant changes in serum biochemistry. ALT levels were increased by ~3% in the DGB25 females; however, the effect was not observed in males, and did not correlate with other changes in liver biochemistry parameters. Brain and pituitary weights were increased in the DGB25 males by 4% ($p<0.01$) and 15% ($p<0.05$), respectively, with a 12% ($p<0.05$) increase in pituitary weight relative to body weight. Similar dose-related trends were not observed in females; therefore, the findings of increased brain and pituitary weights were determined by the authors not to be biologically relevant. Finally, microscopic pathology did not reveal any increased incidence of pathological findings in treated animals relative to unfermented milk controls. A no-observed-adverse-effect level (NOAEL) of 5 mg GABA/kg body weight per day, the highest dose tested, can be determined under these study conditions.

Kato *et al.* (2005) also conducted a 90-day sub-chronic toxicity study of the same GABA-containing fermented milk in rats. The experiment was conducted in the same strain of rat, and at 5 weeks of age, the animals were randomized to 1 of 4 groups (4/sex/group). Each animal received 1 of 4 oral gavage treatment regimens: 20 mL of distilled water (control), 20 mL of unfermented milk (negative control), 20 mL of fermented milk containing GABA at a concentration of 10 mg/100 mL (DGB10), or 20 mL of fermented milk containing GABA at a concentration of 25 mg/100 mL (DGB25). Rats allocated to treatment groups DGB10 and DBG25 received 2 and 5 mg GABA/kg body weight, respectively. Animal housing, GABA treatment, and toxicological endpoints were identical to those detailed for the 28-day study. No significant differences in body weight or food and water intake were reported. Quantitative measurements of biochemical and histological urine parameters revealed no compound-related adverse effects. Urine volume was significantly ($p<0.05$) increased by approximately 30 and 45% in the male rats receiving DGB10 and DGB25, respectively. The increase in urine volume was associated with a slight (approximately 1%; $p<0.05$) decrease in urine specific gravity in the DGB25 group. The changes in urine volume and specific gravity did not occur in females. The authors stated that hypotension has been reported to occur with GABA administration, an effect that is often associated with diuretic effects (Shimizu *et al.*, 1959). Since the observed changes in urine volume were not associated with other adverse effects of urine function, and were not observed in females, the observation was reported to be toxicologically insignificant. In addition, these changes were not noted in the 28-day study. No abnormalities following ophthalmologic analysis were observed. Hemoglobin concentration was significantly lower in the DGB-treated females relative to the unfermented milk controls; however, the observation was slight (<5%; $p<0.05$) and was not observed in males. In the absence of changes for other

indices indicative of anemia, the decrease in hemoglobin concentration observed in females was determined to be toxicologically insignificant. Sporadic decreases ($p<0.05$) in differential leukocyte counts (lymphocyte, neutrophil, and eosinophil) were reported in the DGB25 female animals relative to the unfermented milk group; however, the effects were not dose responsive, were not observed in males, and were not significantly decreased relative to distilled water controls, and therefore, the changes were considered to be a spurious finding and biologically irrelevant. Biochemical indices were unremarkable. Sporadic changes in absolute organ weights were noted with total lung and adrenal weights increased (~10%; $p<0.05$) relative to the unfermented milk controls; however, these changes were not observed in both sexes, were not dose-responsive, and in the case of the adrenals were not significantly changed relative to distilled water controls and hence were considered to be of toxicologically insignificant. Relative pituitary weights were increased in females treated with DGB10 relative to the unfermented milk controls (approximately 20%; $p<0.05$). Again, the observed response was not dose responsive, was not observed in both sexes, was not observed compared to the distilled water controls, and therefore was considered to be a spurious finding. Macroscopic pathology was unremarkable for all groups. From the results of the toxicity study, a NOAEL of 5 mg/kg body weight, the highest dose tested, could be determined for exposure of Sprague-Dawley rats to GABA-containing fermented milk.

Chronic Studies

In reviewing the application for a tolerance exemption for use of GABA as an ingredient in a pesticide, Auxiogrow WP (comprising a mixture of 36.5% L-glutamic acid and 29.2% GABA), the U.S. EPA stated that it reviewed studies from the "open-literature", which demonstrated that chronic GABA administration at up to 1 g/kg/day in rats and dogs was well tolerated and with no signs of toxicity (U.S. EPA, 1997). The studies supporting this information were not identified during the comprehensive search of the published literature.

D. Mutagenicity and Genotoxicity Studies

One study was identified in the literature that assessed the potential mutagenicity of GABA-containing fermented milk products, DGB10 and DGB25, which contained GABA at 10 and 25 mg/100 mL, respectively (Osawa *et al.*, 2005). The Rec assay was utilized to assess the potential mutagenicity of GABA milk using *Bacillus subtilis* strains H17 (Rec+) and M45 (Rec-). Doses of DGB25 were added to paper disks at quantities ranging from 46.9 to 750 mg, and for DGB10 at levels ranging from 18.75 to 300 mg. Both studies were conducted in the presence and absence of metabolic activation. There was no evidence of mutagenicity at either concentration of GABA milk.

E. Studies in Humans

The safety of GABA supplementation has been investigated in a number of studies involving subjects consuming quantities of GABA of up to 120 mg for periods of up to 12 weeks. Approximately 300 hypertensive yet otherwise healthy individuals participated in these studies with no untoward effects reported. Most study reports included additional safety-related endpoints (*e.g.*, full tabulated summaries of all biochemical, hematological, and urinalysis parameters). In addition, 3 studies also were identified in the literature indicating that the consumption of high levels of GABA (up to 18 g/day) for a period of up to 4 days was well tolerated, with only minor side effects noted. A summary of the identified studies of GABA consumption in healthy individuals is presented below.

Cavagnini *et al.* (1980a,b, 1982) conducted a number of studies where GABA was administered orally at quantities of 5 g or more to healthy male and female volunteers. In the first study, 16 females and one male each received a single 5 g oral quantity of GABA. The only observations reported by the authors were a slight burning in the throat occasionally accompanied by a sensation of breathlessness soon after administration lasting a few minutes (Cavagnini *et al.*, 1980a). Cavagnini *et al.* (1980b) also conducted an investigation in which 2 male and 17 female volunteers between 18 and 65 years of age consumed 5 g of GABA dissolved in 150 mL of water. An additional 8 female subjects followed a 4-day regimen of daily GABA consumption, where 18 g of GABA was consumed daily in 4 divided doses, with the last dose being taken 1 hour before a post-study insulin tolerance test (test methodology not indicated). The authors reported that GABA consumption was well tolerated with an occasional report of burning in the throat accompanied by a sensation of breathlessness lasting a few minutes. No change in baseline glucose, pulse rate, or blood pressure was observed in association with the consumption of 18 g/day of GABA over a 4-day period. GABA also was observed not to effect glucose concentrations during an insulin tolerance test. The rational for investigating the effect of GABA on glucose metabolism was unclear as no information suggesting that GABA is suspected to affect glucose metabolism was presented or identified in the literature. In a third study, 12 healthy subjects (3 men and 9 women) each consumed 0 (placebo), 5, or 10 g of GABA dissolved in water on separate days over a 5-day period. Similar to the previous studies, a slight burning sensation in the throat and a sensation of breathlessness lasting a few minutes were reported. In addition, dose-responsive significant ($p<0.01$) increases in immunoreactive insulin and glucagon were observed (60 and 40%, respectively), although the effect was transient and returned to baseline within 180 minutes; however there were no changes in blood glucose levels following GABA consumption (Cavagnini *et al.*, 1982).

Kimura *et al.* (2002) investigated a GABA-containing fermented milk (FGM) in three separate studies involving healthy volunteers. The FGM test material was produced using two strains of lactic acid bacteria (*L. casei* and *L. lactis)* that are capable of converting glutamate to GABA. Following fermentation of the milk, the level of GABA was analyzed and a range of 11.5 to 12.8

mg/ 100 mL was determined. Regular milk was used as the placebo for the second and third tests. The first study was conducted in 8 normotensive men (36.5 ± 9.7 years of age, weighing 75.3 ± 7.6 kg), wherein each subject consumed one 100 mL bottle of FGM (providing approximately 12 mg GABA)/day for 8 weeks. Health interviews were conducted twice during the study, blood clinical chemistry and hematology parameters were measured, and urine samples were assayed for protein, urobilinogen, sugar, and occult blood. The second investigation was a gastrointestinal tolerability study conducted in 12 subjects (6 men and 6 women; 32 ± 6 years of age, weighing 59 ± 8 kg) randomized to 1 of 2 groups, where one group consumed three 100 mL bottles of GABA milk (providing approximately 32 mg GABA/day) and one group consumed an equivalent quantity of regular milk per day within 1 hour after lunch for a period of 1 week. After one week of consumption of GABA or regular milk, the groups crossed over to the opposite study arm for an additional week. The authors monitored defecation, stool quality, overall health, and gastrointestinal symptoms during the study. The third study was conducted in 16 subjects (8 men and 8 women; 31 ± 4 years of age, weighing 60 ± 11 kg) who were divided into 1 of 2 groups, with 1 group receiving a single supplementation of 300 mL of FGM (providing approximately 32 mg GABA/day) and the other receiving regular milk. Similar safety parameters as measured during the first study were examined. The consumption of GABA (approximately 12 mg/person/day or approximately 0.16 mg/kg body weight/day) for 8 weeks (Test 1) was well tolerated, and GABA consumption at amounts 3-fold greater (*i.e.*, 32 mg/person/day or approximately 0.63 mg/kg body weight/day) over a course of one week also was well tolerated. The hematological and clinical chemistry data support the safety of the GABA administered. The only significant change noted was a slight decrease in serum aspartate aminotransferase (AST) (-17%; $p<0.05$) and chloride (-1.9%; $p<0.05$) levels in subjects consuming GABA. In Test 2, the consumption of GABA did not adversely affect defecation frequency or stool characteristics, and there were no abnormal abdominal signs or symptoms. In addition, heart-rate, diastolic and systolic blood pressure were monitored during test 1 and 3; no significant between group differences in these parameters were reported.

Matsubara *et al.* (2002) investigated the tolerability of GABA supplementation in 100 mild hypertensive yet otherwise healthy adults over an 8-week trial period. A 4-week dose-response pilot study was initially conducted in 51 adults (21 men and 30 women; 20 to 70 years of age, weighing between 50.9 ± 2.8 and 53.1 ± 2.7 kg) randomized to 1 of 4 groups receiving GABA at oral doses of 0 (placebo), 20, 40, or 80 mg/day, delivered as 1 or more tablets containing 0 or 20 mg of GABA. The GABA test article used in the study (>99.0% purity) was produced from glutamine using a fermentation refining process. Blood and urine samples were collected at baseline and upon completion of GABA supplementation, and standard clinical chemistry and hematology measurements were obtained. Following 4 weeks of GABA supplementation, measurements of standard safety-related parameters were unremarkable at all doses. The second phase of the study was conducted in 46 hypertensive male and female subjects (21 men and 25 women; 20 to 70 years of age; weighing between 51.3 ± 1.7 and 52.9 ± 1.8 kg). In

the third phase of the study, 49 subjects participated in a tolerability assessment (20 to 70 years of age; number of men and women and weight not provided). In both tests subjects were allocated to 1 of 2 groups receiving 4 placebo or GABA tablets per day (after breakfast for a period of 8 weeks. Plasma GABA levels were measured throughout the study. The results indicated that orally administered GABA was either poorly absorbed and/or was rapidly cleared since daily intake of 80 mg of GABA/person/day did not alter plasma GABA levels relative to control subjects. Hematological, clinical chemistry and urinalysis findings were unremarkable. No issues regarding compliance were noted and adverse effect monitoring revealed no GABA-specific adverse effects. Measurements of blood pressure obtained during the investigations indicated slight yet significance differences in diastolic and systolic blood pressure between groups. Although blood pressure remained above normal in both groups at the end of the study, systolic and diastolic blood pressures were approximately 5% lower ($P<0.05$) in the subjects randomized to the GABA groups relative to the controls.

Inoue *et al.* (2003) conducted a randomized, placebo-controlled, single blind trial in 39 mild hypertensive yet otherwise healthy male and female subjects (23 men and 16 women; 28 to 81 years of age, with average weights of 63.5 ± 2.9 and 69.5 ± 4.3 kg for test and placebo groups, respectively) consuming FGM. The test product used in the study was produced from skim milk fermented with *L. casei* and *L. lactis*. The placebo test article was prepared by adding lactic acid to the skim milk. The level of GABA in the FGM was between 10 to 12 mg/100 mL (providing approximately 0.17 mg GABA/kg body weight/day), and no GABA was detected in the placebo preparation. Subjects were randomized to 2 subgroups, 1 receiving 100 mL of FGM daily at breakfast for 12 weeks, and the other receiving the acidified milk placebo for 12 weeks. Subjects were followed for an additional 2-week post-study period. Blood samples were taken from each subject at baseline and after the completion of the 12-week study period. Standard biochemical, hematological, and urine monitoring were conducted. Two subjects in each group dropped out for reasons that were determined not to be related to the GABA supplementation, and no side effects were reported in either group. Over the 12 weeks of fermented GABA milk consumption, safety endpoint measurements, including heart rate, body weight, hematological and blood chemistry variables, and urine analysis, did not differ between groups. Measurements of diastolic and systolic blood pressure also were obtained. Systolic and diastolic blood pressure decreased over time in both groups; no significant between-group differences in blood pressure (mmHG) were reported during any of the time-points.

Watanabe *et al.* (2002) examined the use of a GABA-enriched Brazilian mushroom, *Agaricus blazei Murill* (AG-GABA), in 14 mild hypertensive yet otherwise healthy subjects. The test article was produced by adding the *Agaricus* fruit body to water and allowing it to self-digest (original article in Japanese, exact meaning was unclear in the English translation) for 17 hours at 50°C. The end product contained 2.7% GABA and the freeze-dried powder was added to opaque capsules for use in the study. Each GABA capsule contained 6.25 mg GABA. Placebo capsules were manufactured to contain a similar compositional content without the GABA. A

9-week open-end pilot study was initially conducted in 10 subjects (study subject demographics not provided). Each subject received 25 mg of GABA delivered as 4 capsules/day. The study was initiated following a 1-week non-supplemented observation period, and a 6-week post-study observation period also was included. Blood serum biochemical samples were taken at Weeks 0 and 9, and a number of biochemical and hematological analyses were performed. Following the pilot study, a double blind comparative crossover test was conducted in subjects consuming AG-GABA over 9 weeks. Fourteen (14) subjects were divided into 2 groups, and following a 1-week pre-study observation period, Group A (45.6 ± 12.2 years of age, weighing 73.1 ± 14.8 kg) received AG-GABA and Group B (46.4 ± 15.4 years of age, weighing 69.0 ± 9.3 kg) received placebo. A 1-week washout period was included before the crossover phase. The subjects consumed AG-GABA twice daily (morning and evening) to provide 25 mg GABA/day. Blood and hematological tests were conducted 3 times (during Week 0, 4, and 9), and the evaluated parameters for blood and hematological examinations were identical to the open test. AG-GABA was well tolerated in both studies and serum biochemical/hematological tests did not reveal any significant changes during the open test or crossover studies. Measurements of systolic and diastolic blood pressure also were monitored throughout the study. No significant differences in blood pressure (mmHg) were observed between the two groups at any time-point.

Kajimoto *et al.* (2003a) conducted a placebo-controlled, double blind study investigating the use of FGM (prepared using *L. casei* and *L. lactis*) in 86 healthy subjects with mild or moderate hypertension. The placebo test article was prepared using skim milk powder and was formulated to contain a similar amount of lactic acid as the GABA milk such that both products were indistinguishable in all sensory aspects. The level of GABA in the FGM was equal to or greater than 10 mg/100 mL, and no GABA was detected in the placebo preparation. The subjects were divided into 2 groups, one receiving 100 mL of FGM/day (approximately 10 mg GABA and providing 0.15 mg/kg body weight/day) and the other receiving the placebo beverage. Subjects were instructed to consume the milk every morning for a period of 12 weeks. The following parameters were measured at varying intervals throughout the study period: clinical inspection and interviews, weight and body mass index (BMI), blood pressure and heart rate, urine indices, and standard blood clinical chemistry and hematology. Eight (8) subjects were excluded for failure to meet blood pressure inclusion criteria on the first study day, and 6 subjects dropped out of the trial for private reasons. Over the course of the study, measurements of body weight and BMI, as well as blood and urine parameters, were unremarkable. Although blood pressure remained above normal in both groups at the end of the study, average systolic and diastolic blood pressures were ~5% ($P<0.01$) lower in the GABA supplementation group relative to the hypertensive controls. No GABA-related adverse effects were reported.

In a second randomized, placebo-controlled, double blind trial, Kajimoto *et al.* (2003b) assessed the effects of GABA in 108 healthy men and women (42 men and 66 women; 46.4 ± 1.7 and 47.1 ± 1.7 years of age and weighing 62 ± 1.4 and 61.3 ± 1.3 kg in the test and placebo groups,

respectively) with high-normal blood pressure. The fermented GABA milk (FGM) was identical to that used by the authors in the previous study (Kajimoto *et al.*, 2003a). No GABA was detected in the placebo milk. The volunteers were divided into 2 groups, with one group consuming 100 mL of FGM (providing approximately 12.3 mg GABA/day) every morning during the 12-week supplementation phase, and the other consuming the placebo drink. A 4-week pre-study (Weeks -4 and -2) and a 4-week post-study (Weeks 14 and 16) observation period also were included in the trial. Weight and BMI were measured. Standard clinical chemistry, hematology, urinalyses and blood pressure monitoring also were conducted at varying time points throughout the study. Following daily GABA administration, no significant compound-related effects on BMI or heart rate were observed. Although blood pressure measurements remained above normal throughout the study period in both groups, average systolic and diastolic blood pressures were up to ~7% ($P<0.05$) lower in the subjects randomized to the GABA supplementation group. Measurements of serum biochemical and hematological parameters were unremarkable and no significant difference in any urinalysis parameters was reported. No GABA-related side-effects were observed during the study.

In a third study, Kajimoto *et al.* (2004) investigated the supplemental use of GABA in 88 male and female hypertensive yet otherwise healthy subjects (31 men and 57 women; 53.8 ± 8.5 and 54.7 ± 8.6 years and weighing 59.7 ± 10.1 and 58.8 ± 9.2 kg for test and placebo groups, respectively) using a randomized, double blind, placebo-controlled, parallel group study design. Following a 2-week observation period, subjects were randomized to 1 of 2 groups receiving 4 placebo or GABA tablets (Otsuka Pharmaceutical Co., Japan; 20 mg GABA/tablet) per day before breakfast for a period of 12 weeks, resulting in 0 or 80 mg GABA/day. A 4-week post-study observation period also was included in the trial. Blood pressure and body weight were measured in all subjects and blood (clinical chemistry, including plasma GABA levels, and hematology) and urine tests were performed. Similar to Matsubara *et al.* (2002), plasma GABA levels after 12 weeks of consuming GABA at a dose of 80 mg/day were not significantly increased relative to controls. A significant but transient change in blood pressure was observed (-5%; $P<0.01$) in subjects receiving GABA compared to those in the placebo group. Although some clinical chemistry values were decreased in the GABA group, all values were within historic control ranges and were considered to be clinically irrelevant. Urinalysis findings were considered unremarkable. No GABA-specific adverse effects were reported by any of the subjects and none of the reported symptoms (cold, headache, diarrhea, loose stool passage, hand-foot-mouth disease in one patient, itching, rash) were deemed by the study investigator(s) to be related to GABA administration.

Using a double blind, placebo-controlled, parallel group design, Yamakoshi *et al.* (2006) studied the tolerability of consuming a GABA-enriched food in 177 hypertensive yet otherwise healthy male and female subjects chosen from the untreated subjects' databank of Soiken Inc. The test products included GABA-enriched low-salt soy sauce (120 mg GABA/8 mL), low-salt soy sauce, and regular soy sauce, with a daily intake of 8 mL of soy sauce by all subjects. The GABA

levels in the low-salt soy and regular soy sauce products were determined to be <1 mg GABA/ 8 mL. The subjects were randomly allocated to study groups receiving GABA-enriched low-salt soy sauce providing 120 mg of GABA/day (48.9 ± 8.9 years of age, weighing 65.9 ± 13.5 kg), low-salt soy sauce (48.1 ± 9.7 years of age, weighing 68.0 ± 14.2 kg), or regular soy sauce (48.9 ± 9.1 years of age, weighing 68.4 ± 13.5 kg). At varying intervals during the study period, blood pressure, heart rate, and body weight were measured, and blood and urine samples were analyzed. After 12 weeks of GABA-enriched soy sauce intake average systolic blood pressures were 4.6 mmHG ($P<0.05$) lower than those in the control subjects consuming regular soy sauce. No change in diastolic blood pressure between groups was noted. Blood pressure measurements remained above normal in all groups at the end of the study. In addition, no significant differences in blood pressure measurements were observed between the subjects in the GABA low salt soy sauce groups relative to the control subjects consuming the low-salt soy sauce at any time-point. There also were some significant changes among the various measured parameters (LDH, albumin, urea nitrogen, and calcium); however, all changes were below 10%, were within the historical reference range, and were deemed by the investigators to be clinically insignificant. The incidence of clinical findings related to adverse effects were similar between groups, and no specific side effect was considered compound-related.

In healthy individuals, GABA supplementation *via* GABA tablets or GABA-supplemented foods (10 to 120 mg of GABA/person/day) for up to 12 weeks in duration was well tolerated. In addition, short-term oral doses of up to 18 g GABA also were well tolerated in human supplementation studies. Based on observations from several studies, daily GABA consumption is associated with modest trend towards normal blood pressure in hypertensive subjects; however, there is no clear dose-response relationship for this effect, and the maximal effect, although statistically significant in many studies, is modest (*i.e.*, maximum decreases of 5 to 7%) when compared to changes in the control subjects. Importantly, the effect also appears to be limited to hypertensive individuals as studies in normotensive individuals at low (10mg/person/day for 8 weeks) and high doses (5 to 18 g for 1 to 4 days) did not affect blood pressure (Kimura *et al.*, 2002; Cavagnini *et al.*, 1980a,b). In addition, most studies utilize GABA fermented beverages as the test article, and it is therefore unclear if slight reductions in blood pressure reported in hypertensive subjects are attributed to GABA. Finally, the effect of GABA on blood pressure in hypertensive subjects appeared to be time-dependent and typically required at least 2 weeks of continual daily use before significant reductions were observed, and the effects are not maintained upon discontinuation of GABA supplementation.

F. GABA and Growth Hormone Secretion

The use of GABA in dietary supplements is frequently targeted to the body building market, with purported claims of increasing growth hormone (GH) secretion. Serving sizes of 3 to 10 g of GABA are usually recommended for this effect. Evidence of increased GH secretion in humans following the oral administration of GABA has been reported in the literature. In studies

conducted by Cavagnini *et al.* (1980a,b), single oral GABA doses of 5 g were associated with rapid increases in GH plasma levels, which peaked at 3 hours post-dosing. Maximum plasma levels were increased by approximately 5-fold, with GH concentrations returning to baseline within 180 minutes. Meanwhile, the administration of 18 g GABA daily for 4 days to 8 healthy subjects caused a significantly blunting of the overall GH release. This result implies that GH secretion by GABA may be down-regulated by high-dose and consecutive administration.

Powers et al. (2008) also reported that the consumption of large quantities of GABA resulted in significant increases in circulating levels of GH. Eleven resistance-trained men (18 to 30 years) participated in the randomized, double-blind, placebo-controlled, crossover study. Subjects consumed either 3 g of GABA or sucrose placebo, which was then followed by resting or resistance exercise sessions. Fasting venous blood samples were then acquired at time 0, 15, 30, 45, 60, 75, and 90 minutes post-GABA or placebo administration. GABA consumption resulted in an increase in peak serum concentrations of both immunoreactive (ir) and immunofunctional (if) GH levels by approximately 4-fold ($P<0.05$). ifGH and irGH area under the curve values (AUC; t = 0 to 90 minutes) also were increased by 3-fold over the 90-minute period ($P<0.05$ for irGH only); however, the increases in irGH and ifGH serum concentrations observed following GABA consumption were significantly less than those observed following exercise, where increases in peak concentrations of ifGH and irGH were increased by 16-fold above the levels in resting subjects consuming the placebo. Similarly, AUC values were increased 14-fold relative to those reported in subjects at rest.

Based on the available data, a threshold for GABA-induced increases in GH secretion could not be determined; however, GABA-induced increases in GH appears to be limited to the consumption of large quantities of GABA (>3 g; 34 mg/kg body weight), and although the increases that have been reported appear large (3- to 5-fold), they are clearly within the normal physiological range, since the increases are well below those observed in the same subjects during exercise (Powers et al., 2008).

The physiological role of GABA in the regulation of GH secretion is unclear; however, the mechanism for the effect appears to be mediated at a paracrine level, as enzymes responsible for GABA production (glutamate decarboxylase), transport (vesicular GABA transporter), and each of the GABA receptors (GABA-a, -b, -c) have been identified *via* immunohistochemistry, and reverse transcription polymerase chain reaction (RTPCR) analysis of human and rodent post-mortem pituitary tissues (Gamel-Didelon *et al.*, 2002; End *et al.*, 2005). Furthermore, unlike effects in neurons, *in vitro* studies conducted using rodent pituitary cells indicate that GABA signaling is rapidly desensitized in these cells (Gamel-Didelon *et al.*, 2003). This observation is consistent with the study by Cavagnini *et al.*, (1980b) where a significant blunting of the GH induction was observed following repeat administration of 18 g of GABA for 4 days. In addition, the rapid desensitization of pituitary GABA signaling and the rapid clearance of exogenous GABA from the circulation ($t_{1/2}$ = ~20 minutes) are consistent with the transient

induction and rapid clearance (return to baseline) of GH from the plasma that is observed in humans following oral GABA consumption. Given the fact that stimulation of the GABA-GH pituitary system is controlled in a paracrine manner, and the observation that orally administered GABA displays poor bioavailability and a short plasma half-life, it is not surprising that the consumption of extremely high quantities (5 to 18 g) of GABA are required for GH induction in humans and rodents.

The ability to increase GH secretion is not unique to GABA, and it is also interesting to note that similar increases in GH plasma levels are observed in association with exercise and with the consumption of arginine, an amino acid routinely consumed in the diet, at high doses (Paddon-Jones *et al.*, 2004; Collier *et al.*, 2005; Kanaley, 2008). For example, as reported by Collier *et al.* (2005), the consumption of arginine in high quantities (5, 9, or 13 g) resulted in significant increases in GH AUC values by as much as 3-fold at the highest dose.

Based on the following observations, GABA, when used as an ingredient in food under the intended conditions of use described herein, is not expected to display GH stimulatory activity: that GABA-induced GH secretion is transient; is associated with rapid desensitization of GABA signaling in pituitary cells; requires large oral doses of between 3 to 18 g to induce effects; that the increases reported in the literature are within the normal physiological range and below those reported during exercise; and that similar increases in GH secretion also are reported in association with the consumption of free amino acids (arginine). This conclusion is further supported by supplementation studies where the consumption of 80 mg of GABA on a daily basis did not increase GABA plasma levels above baseline. Furthermore, the safe use of GABA under the intended conditions of use also is supported by the lack of adverse effects in toxicity studies conducted in rats, a species that like humans also is responsive to GABA-induced GH secretion, at doses corresponding to or in excess of the proposed uses.

G. Information Pertaining to the Safety of the Bacterial Enzymes

Organisms from the genus *Lactobacillus* are Gram-positive, non-spore-forming rods or coccobacilli. To date, 136 species and 27 subspecies of *Lactobacillus* have been identified (Euzéby, 2007). The bacteria are strictly fermentive organisms and can be aerotolerant or anaerobic, aciduric or acidophilic, and display complex nutritional requirements (*i.e.,* requirements for carbohydrates, amino acids, peptides, fatty acid esters, salts, nucleic acid derivatives, and vitamins) (Bernardeau *et al.*, 2006). Due to their fermentation capabilities, *lactobacilli* have been used to alter the texture and or flavor of a large variety of foods (*e.g.*, beer, wine, cheese, yogurt, cured meats, *etc.*) for well over a millennia. More recently *lactobacilli* have received increased popularity in association with their use as probiotic foods. In 2000-2001, a workshop that included panel members with expertise in clinical practice, microbiology, intestinal microecology, pathogenicity, nutrition, toxicology, and public health was convened to discuss the safety of *lactobacilli* and *bifidobacteria* used as probiotics in foods, and to review criteria for the evaluation of the safety of new probiotics (Borriello *et al.*, 2003). It was

reported that cases of infection due to *lactobacilli* and *bifidobacteria* are rare and that increased consumption of probiotic products containing *lactobacilli* and *bifidobacteria* has not led to increases in these infections in consumers (Borriello *et al.*, 2003). It also is generally accepted that *lactobacilli* and *bifidobacteria* are safe and have a long history of safe consumption (Holzapfel *et al.*, 1998; Vanderhoof and Young, 1998; Saarela *et al.*, 2002; Borriello *et al.*, 2003; Picard *et al.*, 2005; Boyle *et al.*, 2006).

The safety of the *Lactobacillus* genus has also been extensively evaluated by Bernardeau *et al.* (2006) and the authors stated that "no cases of collective food borne disease have been reported in healthy people or farm animals following the ingestion of food or feed containing *Lactobacilli*". This view is also supported in a review by Adams (1999) regarding the safety of industrial lactic acid bacteria. Adams (1999) concluded that based on the long history of consumption, in conjunction with the current available epidemiological, clinical and acute toxicity data, that lactic acid bacteria commonly occurring in fermented foods and used in probiotics are safe.

During a screening process of various lactic acid bacteria, PFI identified *L. hilgardii K-3* to be a significant GABA-producing strain, which due to its high glutamate decarboxylase metabolic capacity, is capable of converting large amounts of glutamate to GABA during large scale fermentation. The bacterial strain was originally isolated from kimchi, which are fermented Korean pickles. *L. hilgardii K-3* is a bacterial strain from the *Lactobacillaceae* family of the genus *Lactobacillus*. The species is not currently listed as a bacterial source approved for use in foods or in the production of foods, and therefore information supporting that the use of *L. hilgardii K-3* is safe under the intended conditions of were evaluated to establish the safety of *L. hilgardii* K-3 for use the manufacture of GABA.

The presence of *L. hilgardii* in foods produced by fermentation is well established and the organism has a long history of consumption. For example, *L. hilgardii* was originally isolated and characterized from California wine by Douglas and Cruess in 1936 (Douglas and Cruess, 1936). A number of lactic acid bacteria, including various strains of *L. hilgardii*, are responsible for malolactic fermentation, an important step in wine making. Several strains of *L. hilgardii* have been isolated from a number of fermented grape sources used in the production of wine, as well as from tibi grains and sugar beets (Sohier *et al.*, 1999; NCIMB, 2007). Rodas *et al.* (2005) isolated 178 bacterial strains from a microbiological survey of 32 grape musts and wine samples belonging to the Utiel-Requena and Juilla Origin Denominations in Spain. The authors discovered that the majority (~40%) of *Lactobacilli* in wine belong to the *L. hilgardii* species. Finally, *L. hilgardii* has been identified by Baruzzi *et al.* (2000) as a strain associated with ricotta cheese fermentation, and up to 10% of the total microflora in the cheese during the ripening process were identified as *L. hilgardii* after 7 months of ripening.

The *Lactobacillus* genus can be considered non-pathogenic and non-toxigenic; however, some species of *Lactobacillus*, including *L. hilgardii*, are capable of producing biogenic amines such

as tyramine, histamine, putricene, and phenylethylamine. The presence of biogenic amines in wine, cider, cheeses, and cured meats due to the presence of *Lactobacillus* is common (Suzzi and Gardini, 2003; Ferreira and Pinho, 2006; Garai *et al.*, 2006; Landete *et al.*, 2007), and generally does not result in adverse effects or toxicity. Although rare, toxicity due to high levels of biogenic amines (usually histamine) has been reported to occur in healthy individuals, and symptoms generally involve headache, palpitations, flushing, and to a lesser extent nausea, diarrhea, and erythema (Becker *et al.*, 2001; Ohnuma *et al.*, 2001; Miki *et al.*, 2005). For histamine toxicity, the hazardous intake level is believed to be ≥50 mg/100 g of food (Lehane and Olley, 2000), although this threshold is likely lower in subjects with genetic or drug-induced impairment of biogenic amine metabolism due to deficiencies in, or the inhibition of, enzymes catalyzing their decarboxylation. Costantini *et al.* (2006) examined 133 strains of bacteria isolated from musts and wine from various regions in Italy to identify the bacteria strain(s) responsible for biogenic amine (histidine, tyramine, and putrescine) production. Only 1 of 11 *L. hilgardii* strains was identified as expressing histidine decarboxylase mRNA (*hdc*), the gene encoding the enzyme responsible for the conversion of histidine to histamine. This strain also was shown to be capable of histamine production. All *L. hilgardii* strains were negative for genes encoding ornithine decarboxylase and tyrosine decarboxylase, the genes encoding the enzymes responsible for putrescine and tyramine respectively. In contrast, Landete *et al.* (2005) investigated the ability of 136 bacteria strains isolated from wine to determine which strains were responsible for histamine production, and determined that all 4 *L. hilgardii* strains were histamine producers. In addition, of the bacteria isolated and determined to be histamine producers, *L. hilgardii* and *Pediococcus parvulus* were identified as the principle bacteria responsible for the occurrence of histamine in wine. Under optimal conditions histamine production for *L. hilgardii* ranged between 39 to 297 mg/L.

Moreno-Arribas *et al.* (2000) isolated a number of bacteria from tyramine-containing wines and discovered that the primary tyramine producer was *Lactobacillus brevis*, and no *L. hilgardii* strains were detected in the tyramine-containing wine. The authors also investigated a large number of commercially-available (isolated from various fermented grape products) lactic acid bacteria strains for their tyramine producing capacity and discovered that only 1 strain in 17 *L. hilgardii* strains could produce tyramine. Similar observations for tyramine production by *L. hilgardii* and *L. brevis* were observed by Landete *et al.* (2007) where the authors identified 2 strains from 8 strains of *L. hilgardii* as producers of tyramine and phenylethylamine, and average production of these biogenic amines under optimal growth conditions ranged from 120 to 535 mg/L.

Although it is clear that strains of *L. hilgardii* can produce a variety of biogenic amines, contamination of PFI's GABA in a manner that would be toxicologically relevant is unlikely. A detailed compositional analysis of the GABA ingredient was performed (see Appendix B; Table B-3) indicating that the level of free amino acid contamination is low, and with the exception of glutamic acid, all amino acids are below 0.5%, and many of the biogenic amine precursors

(histidine, tyramine, and phenylalanine) were detected at a concentration of ≤0.04%. In addition, PFI has tested their GABA ingredient for the presence of histamine using HPLC analysis and has confirmed that the product is free of this biogenic amine [see Appendix B, Attachment B-3 for the original copy of the analytical results of histamine analysis (presented in Japanese only)].

Lactic acid bacteria (L*actobacillus buchneri, Oenococcus oeni,* and *L. hilgardii*) are often used to develop flavors in wine *via* a process called malolactic fermentation, a stage of wine-making that is performed subsequent to alcoholic fermentation during wine production. Periodically, malolactic fermentation is associated with the formation of the mutagenic compound, ethyl carbamate in a process that is assumed to occur in association with L-arginine catabolism (Mira De Orduña *et al.*, 2001). Lactic acid bacteria that express significant levels of arginine deaminase are believed to catalyze this process *via* the formation of L-citrulline. The L-citrulline is then released from the bacteria where the compound slowly reacts with the ethanol present in the wine producing ethyl carbamates. Given the slow production of ethyl carbamate from citrulline in wine, studies specifically demonstrating ethyl carbamate production by *L. hilgardii* are not available; however, a number of experiments have shown that some strains of the organism can actively degrade L-arginine to citrulline (Rodríguez *et al.*, 2007; Arena *et al.*, 2002; Azevedo *et al.*, 2002), and in theory, wines produced using these strains could be susceptible to ethyl carbamate production if significant concentrations of L-arginine remain following alcoholic fermentation. It is unclear if the strain of *L. hilgardii* used in the production of GABA (*L. hilgardii* K-3) expresses a functional arginine deaminase enzyme; however, a significant source of arginine is not present during GABA fermentation, nor is ethanol used during the manufacturing of the ingredient; thus, the formation of ethyl carbamate during GABA production is not expected. This hypothesis is supported by studies conducted by PFI at the Japanese Food Research Laboratory, the results of which indicated the absence of ethyl carbamate in the final product at a detection limit of 0.01 ppm [see Appendix B, Attachment B-4 for a copy of the results of ethyl carbamate analysis

In addition, although the absence of *L. hilgardii* K-3 in the final product is ensured by a filter sterilization step, which utilizes a 0.6 micron filter, test results from the manufacturer confirm that no *L. hilgardii* is present in the food grade GABA.

Therefore, the safe use of *L. hilgardii K-3* in the production of GABA for use in food is based on the following observations: from published information that the *L. hilgardii K-3* strain was isolated from kimchi, which are consumed in the human diet; the fact that the species (*L. hilgardii*) has a long history of consumption *via* its presence in fermented foods; and that *L. hilgardii* is the most prevalent species of lactic acid bacteria identified in wine. This basis of safe use of L. hilgardii K-3 is corroborated by the negative results of PFI's histamine and ethyl carbamate testing.

The above conclusion is consistent with the positive United States Food and Drug Administration (FDA) ruling on the GRAS affirmation of a mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis.* The FDA stated that the enzyme mixture derived from *B. licheniformis* was GRAS "based on published information establishing that *B. licheniformis* is a widely recognized as a harmless contaminant found in many foods" (U.S. FDA, 1983).

H. Summary and Basis for GRAS

The GRAS status of GABA derived from *L. hilgardii* K-3 fermentation of L-glutamate under the intended conditions of use described herein is based on the following evidence:

1. PFI's GABA ingredient is manufactured in-line with current Good Manufacturing Practices (cGMP) using appropriate food-grade materials.

2. PFI's GABA ingredient meets acceptable food-grade specifications

3. GABA exists naturally in many different foods and therefore has a long, well-established background of dietary consumption by humans, with an average intake of GABA from its natural occurrence estimated to be approximately 80.20 and 135.56 mg/person/day in the Japanese and U.S diets respectively, which is within the range of the estimated intakes of GABA under the intended conditions of use of PFI's GABA ingredient. GABA also has been added to foods in Japan for over 20 years at levels up to 280 mg/50 g serving, which further supports the safe use of PFI's GABA as defined herein.

4. Generally available data indicating that GABA is metabolized to innocuous substances that are readily cleared from body.

5. Studies from the public domain indicating that GABA does not cross the BBB from the systemic circulation, which ensures that orally administered GABA will not display neuropharmacological activity.

6. Investigators establishing that a NOAEL of 5 mg/kg body weight/day, the highest dose tested, could be established for the administration of a fermented GABA milk to rats.

7. Published studies demonstrating that GABA supplementation was not associated with adverse health effects following daily GABA intakes up to 18 g for 4 days or following long-term daily intakes of 120 mg for up to 12 months.

8. The results of analytical data and information obtained from the literature indicating that *L. hilgardii* K-3 is safe for use in the manufacture of GABA for use in food.

9. Finally, a comprehensive package of data were reviewed by a panel of experts, qualified by scientific training and experience to evaluate the safety of GABA as a component of food, who unanimously concluded that the proposed uses of GABA are safe and suitable and would be GRAS based on scientific procedures.

The GRAS status of GABA under the intended conditions of use described herein is supported by the following evidence:

1. An acute and a subchronic toxicity study conducted using PFI's GABA ingredient at doses of 1,000 and 200 mg/kg body weight respectively (the only doses tested) were without evidence of toxicity;

2. The EPA reviewed toxicity studies in rodents and dogs and concluded that GABA was well tolerated without signs of toxicity at doses up to 1g/kg body weight for a period of up to 1 year.

Therefore, Pharma Foods International has concluded that its GABA ingredient is GRAS under the intended conditions of use on the basis of scientific procedures.

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Table of CFR Sections Referenced (Title 21—Food and Drugs)		
Part	**Section §**	**Section Title**
101—Food labelling	101.12	Reference amounts customarily consumed per eating occasion
170—Food additives	170.3	Definitions
	170.30	Eligibility for classification as generally recognized as safe (GRAS)
172—Food additives permitted for direct addition to food for human consumption	172.854	Polyglycerol esters of fatty acids.
175—Indirect food additives: Adhesives and components of coatings	175.300	Resinous and polymeric coatings
177—Indirect food additives: Polymers	177.1210	Closures with sealing gaskets for food containers
	177.1520	Olefin polymers
	177.1655	Polysulfone resins
	177.2910	Ultra-filtration membranes

Appendix A

APPENDIX A

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF GABA FOR USE AS AN INGREDIENT IN FOOD

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INTRODUCTION

At the request of Pharma Foods International Co., Ltd. (PFI), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was convened to conduct a critical and comprehensive evaluation of the available pertinent data and information on PHARMAGABA, a *gamma*-amino butyric acid (GABA) ingredient derived from L-glutamate, and determine whether the proposed uses of PHARMAGABA (>80% purity) as a food ingredient would be Generally Recognized as Safe (GRAS) based on scientific procedures. The Panel consisted of the below-signed qualified scientific experts: Prof. Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University, Medical College of Virginia), Prof. Stephen L. Taylor, Ph.D. (University of Nebraska), and Prof. William J. Waddell, M.D. (University of Louisville School of Medicine). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment A-1.

The Panel, independently and collectively, critically evaluated a comprehensive package of scientific information and data provided by PFI and compiled by Cantox Health Sciences International (Cantox). In addition, the Panel evaluated other information deemed appropriate or necessary, including scientific data of GABA complied from the literature and other published sources by Cantox through January 2007. The information evaluated by the Panel included data pertaining to the method of manufacture and product specifications of PHARMAGABA, supporting analytical data, current uses of GABA, intended use levels of PHARMAGABA in specified food products, consumption estimates for all intended uses, and a comprehensive assessment of the available scientific literature pertaining to the safety of GABA.

Following critical evaluation of such data and information, the Panel convened on 18 May 2007 and unanimously concluded that the proposed uses in traditional foods described herein for PHARMAGABA, manufactured consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food-grade specifications, are safe and suitable. The Panel further concluded that these uses are GRAS based on scientific procedures. A summary of the basis for the Panel's conclusions is provided below.

MANUFACTURING AND COMPOSITION

PHARMAGABA is manufactured by a fermentation process that utilizes *Lactobacillus hilgardii* K-3 (*L. hilgardii* K-3) to catalyze the conversion of L-glutamate to GABA. Initially, the pre-fermentation broth is prepared by adding the appropriate substrates to water inside a sealed fermentation vessel, followed by sterilization and cooling prior to the addition of the *Lactobacillus* strain for fermentation. Once fermentation is complete, the mixture is sterilized and then undergoes a series of concentration and filter sterilization steps to produce a highly-concentrated GABA solution. The GABA is then precipitated out of solution by spray-drying, followed by two consecutive steps using a magnetic bar that removes any particulate impurities in the powder. The GABA powder is then sifted before being stored in aluminum pouches. The final product is a minimum of 80% pure GABA and conforms to the established product specifications listed below in Table 1.

Table 1 Product Specifications for PHARMAGABA

Specification Parameter	Specification	Method of Analysis
Appearance	White to light-yellow powder	Visual
gamma-Aminobutyric acid (GABA)	>80%	HPLC, based on Bianchi *et al.*, 1999
Moisture (Loss on drying)	<5%	105°C, 5 hours, based on JSSFA, 2000, p. 29
Ash	<10%	550 to 600°C, 5 hours, without sulfuric acid, based on JSSFA, 2000, p. 7
Total Heavy Metals (as Pb)	<10 ppm	Sodium sulfide colorimetry, based on JSSFA, 2000, p. 24
Lead	<0.5 ppm	Atomic Absorption Spectroscopy
Arsenic	<2 ppm	DDTC-Ag Luminosity absorbance, based on JSSFA, 2000, p. 25
Total Aerobic Counts	<1,000 CFU/g	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35
Yeast and Mold	<300 CFU/g	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35.
Coliform/*Escherichia coli*	Negative	Microbial Limit Tests, based on JSSFA, 2000, p. 32-35.

CFU = colony-forming units; DDTC-Ag = silver diethyldithiocarbamate; HPLC = high-performance liquid chromatography; JSSFA, 2000 = Japan's Specifications and Standards for Food Additives (7th ed.)

The Panel reviewed batch analysis data submitted by PFI and concluded that a consistent product can be produced. Representative lots are routinely assayed to ensure compliance with the final product chemical, physical, and microbiological specifications. All equipment and processing aids (*i.e.,* pH-adjusting agents) used in the manufacture of the ingredient are appropriate for food use. The results of studies of the stability of PHARMAGABA indicated that the ingredient is very stable when stored under cool dry conditions for up to 2 years, and also under the conditions of intended use in foods [*i.e.*, at neutral pH under elevated temperatures (120°C), as a 5% solution in water under elevated temperatures (120°C), and at over a broad pH range (2 to 9) at elevated temperatures (100°C)].

A detailed compositional analysis also was performed on PHARMAGABA to characterize the ash, monoglyceride, dietary fiber, total saccharide, and trace mineral, dipeptide, and free amino acid content of the ingredient. Total acid hydrolyzed amino acid levels also were measured. Ninety percent (90%) of the total ash is accounted for by sodium chloride. No minerals at levels of toxicologic concern were noted, and iron levels were low at 0.15 mg/100 g GABA. The mass balance for total dipeptides and free amino acids analyzed *via* high-performance liquid chromatography (HPLC) corresponded to 100% of the total acid-hydrolyzed amino acid content of the material, indicating that the product is free of protein.

INTENDED CONDITIONS OF USE AND ESTIMATED EXPOSURE

PFI intends to market PHARMAGABA as a food ingredient in the United States in a variety of food products including beverages and beverage bases, chewing gum, ready-to-drink coffee and tea products, and candy at levels providing from 30 to 200 mg GABA/serving. The individual proposed food uses and use levels for PHARMAGABA are summarized in Table 2. Food codes representative of each proposed food use were chosen from the National Center for Health Statistics' (NCHS) 2003-2004 National Health and Nutrition Examination Survey (NHANES) (CDC, 2006; USDA, 2006) and were grouped in food use categories according to Title 21, Section §170.3 of the *Code of Federal Regulations* (U.S. FDA, 2008a).

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

Food Category	Proposed Food Uses	GABA Level (mg/serving)	Serving Size (g or mL)	Use Levels of PHARMAGABA (%)
Beverages and Beverage Bases	Energy, Sport, and Isotonic Drinks	30 to 200	500	0.04 to 0.048
	Meal Replacement Drinks	30 to 100	100	0.1 to 0.12
Chewing Gum	Chewing Gum	10 to 100	3	3.33 to 3.996
Coffee and Tea	Coffee, Ready-to-Drink	Up to 100	240*	0.042 to 0.050
	Tea, Ready-to-Drink	Up to 100	240*	0.042 to 0.050
Hard Candy	Hard Candy (Including Mints)	30 to 70	30	0.23 to 0.276
Soft Candy	Chocolate Confections	30 to 100	100	0.1 to 0.12

*RACC = Reference Amounts Customarily Consumed per Eating Occasion as per 21 CFR §101.12 (U.S. FDA, 2008b).

Approximately 37.2% of the total U.S. population was identified as consumers of PHARMAGABA from the proposed food uses (3,073 actual users identified). Consumption of PHARMAGABA-containing foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of GABA of 47.03 mg/person/day (0.73 mg/kg body weight/day) and 126.30 mg/person/ day (1.97 mg/kg body weight/day), respectively (Tables 3 and 4). The 90th percentile all-person and all-user intakes of GABA by the total population from all proposed food uses of PHARMAGABA were 150.19 mg/person/day (2.40 mg/kg body weight/day) and 266.40 mg/ person/day (4.22 mg/kg body weight/day), respectively.

Table 3	Summary of the Estimated Daily Intake of GABA from All Proposed Food Uses of PHARMAGABA in the U.S. by Population Group (2003-2004 NHANES Data)						
Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-User Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infants	0 to 2	16.5	153	9.46	17.48	55.86	177.10
Children	3 to 11	36.1	465	28.91	96.00	72.91	144.00
Female Teenagers	12 to 19	40.1	398	37.59	139.86	108.75	215.34
Male Teenagers	12 to 19	38.2	382	65.19	186.90	148.58	294.00
Female Adults	20 and Up	40.9	871	48.27	159.58	127.46	256.58
Male Adults	20 and Up	41.7	804	55.48	192.00	147.82	349.87
Total Population	All Ages	37.2	3,073	47.03	150.19	126.30	266.40

At 41.7%, male adults were identified as the greatest percentage of users of the population groups, followed by female adults at 40.9% and female teenagers at 40.1%, while infants were identified as the lowest percentage of users of any population group at 16.5%. When mean consumers were assessed, the greatest mean all-person and all-user intakes of GABA on an absolute basis were male teenagers, at 65.19 and 148.58 mg/person/day, respectively (corresponding to 1.04 and 2.37 mg/kg body weight/day). On a body weight basis, the mean all-person intake of GABA was highest in male teenagers (1.04 mg/kg body weight/day), while the mean all-user intake was highest in infants (4.59 mg/kg body weight/day).

When heavy consumers (90th percentile) were assessed, all-person and all-user intakes of GABA from all proposed food uses of PHARMAGABA were determined to be greatest in male adults (192.0 and 349.87 mg/person/day, respectively).

Table 4	Summary of the Estimated Daily per Kilogram Body Weight Intake of GABA from All Proposed Food Uses of PHARMAGABA in the U.S. by Population Group (2003-2004 NHANES Data)						
Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-User Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infants	0 to 2	16.5	153	0.78	1.56	4.59	14.89
Children	3 to 11	36.1	465	0.98	3.21	2.48	5.83
Female Teenagers	12 to 19	40.1	398	0.64	2.44	1.85	3.54
Male Teenagers	12 to 19	38.2	382	1.04	3.03	2.37	5.19
Female Adults	20 and Up	40.9	871	0.69	2.20	1.81	3.83
Male Adults	20 and Up	41.7	804	0.66	2.15	1.75	3.85
Total Population	All Ages	37.2	3,073	0.73	2.40	1.97	4.22

On a body weight basis, children and infants were identified to have the greatest all-person and all-user 90th percentile intakes of GABA, respectively, with values of 3.21 and 14.89 mg/kg body weight/day, respectively (Table 4). It should be noted, however, that the specified PHARMAGABA food uses are not intended to be marketed to infants; thus, the actual infant consumption of GABA is expected to be highly limited, and although an estimate of the consumption of GABA on a body weight basis in infants from all proposed food uses has been included for completeness of this report, it is considered to be a gross over-estimate of the actual expected intake of GABA by infants from its addition to food. This is supported by the fact that the lowest percentage of users, as well as the lowest intakes on an absolute basis, were determined to be in children and infants.

INFORMATION TO SUPPORT THE GRAS STATUS OF PHARMAGABA

The basis for determining the safety of PHARMAGABA includes data demonstrating that GABA is an endogenous molecule, that exogenous GABA does not readily cross the blood-brain barrier, and that GABA has an established background of dietary consumption in the typical human diet, including use as a supplement ingredient, and that GABA has been added to a number of foods in Japan for at least 20 years at levels up to 280 mg/serving without any adverse effects on human health. Additionally, the safety of PHARMAGABA is supported by the fact that GABA supplementation has been investigated in a number of human studies in which it was demonstrated to be without any adverse effects, including a recently conducted placebo-controlled study in healthy subjects at doses up to 120 mg/person/day for 12 months. These data are supported by information obtained from the published literature detailing the metabolic fate of orally administered GABA in rodents, as well as by the results of animal toxicity studies demonstrating no adverse effects following oral administration of GABA. Moreover, PFI provided the results of an acute and a 28-day toxicity study of PHARMAGABA in rats at doses of 1,000 and 200 mg/kg body weight/day, respectively, the results of which were unremarkable. Exposure to GABA in food also has been reviewed by the U.S. Environmental Protection Agency (EPA), who stated that chronic exposure to high levels of GABA in rodents was well tolerated and without evidence of toxicity. In addition, *L. hilgardii*, the bacterial source of the enzyme used to produce GABA from L-glutamate, is a non-pathogenic bacteria species, and has been reported to be present in a number of commonly-consumed foods such as cheese, wine, port, and brandy. A weight of evidence approach to these data strongly support the safety of the proposed uses of PHARMAGABA and the GRAS status based on scientific procedures. A summary of the evidence is provided below.

Background Dietary Consumption of GABA

GABA exists naturally in many different foods at low levels, and in higher levels in fermented food products. Examples of GABA-rich foods include tomatoes, potatoes, melons, and the traditional Korean and Japanese food, kimchi, which have been reported to contain from 27.5 to 74.5 mg GABA/100 g food product, and green tea leaves have been reported to contain as

much as 100 to 200 mg of GABA/100 g on a wt/wt basis (Hayakawa *et al.,* 1997; Matumoto *et al.*, 1997; Akastu, 2000). Other foods are likely to contain appreciable amounts of GABA as a result of the processing methods used to obtain them (*e.g.*, lactic acid-fermented foods, such as cured meats and cheeses); therefore, background exposure to GABA from a typical North American diet is expected, and the intake of GABA under the conditions of intended use is comparable to typical dietary exposure from GABA-containing foods.

Many GABA-enriched foods have been launched onto the Japanese market over the past 20 years with positive consumer reception. Products that currently are enriched with GABA in Japan include tea, germinated rice products, pickles, fermented milk, and chocolate, with GABA contents ranging from approximately 10 mg/100 g in germinated rice to 280 mg/50 g in chocolate. Moreover, GABA was identified as a dietary ingredient in a number of dietary supplement products currently available on the U.S. market at levels ranging from 100 to 750 mg/capsule or tablet and with recommended intakes of GABA typically around 750 mg/person/day, although doses as high as 1,500 to 5,000 mg/day have been indicated for some products, without recommended durations for use.

Absorption, Distribution, Metabolism, and Excretion of GABA

There is limited information detailing the absorption and pharmacokinetic properties of orally administered GABA. Evidence of specific GABA transporters in the rat jejunum has been reported (Nácher *et al.*, 1994); however, the maximum plasma levels of GABA following oral administration of GABA in rats were 20-fold less than those observed following intraperitoneal administration of the same dose, suggesting that absorption and/or bioavailability in rodents (and probably humans) is low (van Gelder and Elliott, 1958). The pharmacokinetics of GABA were demonstrated to be similar among rats, rabbits, and cats, with rapid clearance rates and half-lives of approximately 20 minutes. The tissue distribution of radiolabeled GABA following systemic administration was similar in the rat and mouse, where GABA was distributed primarily to the liver, kidneys, and muscle. In the mouse, significant GABA levels also were detected in the urinary bladder, gastrointestinal wall, pituitary gland, and cartilage of the spine, ribs, and trachea; however, the GABA radioactivity rapidly diminished post-injection (van Gelder and Elliott, 1958; Hespe *et al.*, 1969). It should be noted, however, that the methodology used to measure GABA radioactivity in these studies was non-qualitative, and information distinguishing radioactivity derived from GABA *versus* metabolites of GABA, or potential bacterial degradation products could not be determined. No evidence of GABA bioaccumulation or organ specific retention was observed in any of the reviewed studies[1]. No information detailing the absorption and pharmacokinetics of GABA in humans was identified in the published literature.

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[1] Retention of radioactivity in the Harder's glands was noted during autoradiography studies by Hespe *et al.* (1969); however, this organ is not relevant to humans.

GABA is an endogenous compound, and given its importance as a neurotransmitter, metabolism of the molecule has been well characterized in humans and animals. The liver is considered to be the primary metabolic site of extra-cerebral GABA, and rats display a large capacity for GABA uptake. For example, *ex vivo* liver perfusion concentrations had to be increased 60-fold above baseline plasma levels (84 ng/mL) before saturation of GABA uptake occurred (Schafer *et al.*, 1981; Ferenci *et al.*, 1988). The catabolism of GABA occurs exclusively *via* GABA transaminase where the compound is used as a carbon source in the tricarboxylic acid cycle (TCA), resulting in carbon dioxide (CO_2) as the primary waste product (Ferenci *et al.*, 1988); thus, GABA is essentially utilized as an energy source by the body, and is metabolized to innocuous compounds.

Based on an extensive body of evidence, the ability of the blood-brain barrier (BBB) to prevent GABA permeation from the plasma to the brain, although not absolute, is substantial and not significantly affected by exogenously administered GABA (van Gelder and Elliott, 1958; Hespe *et al.*, 1969; Kuriyama and Sze, 1971; Oldendorf, 1971; Frey and Löscher, 1980; Krantis, 1984; Al-Sarraf, 2002; Al-Awadi *et al.*, 2006). For example, in the rat, a 1,250-fold increase in the dose of GABA administered intraperitoneally resulted in an increase in the levels of GABA in the cerebrospinal fluid (CSF) of only approximately 30-fold. The poor dose-response relationship between the administered dose and GABA permeation across the BBB also was observed in radiokinetic studies, where increases in plasma concentrations of GABA displayed little effect on the overall permeation rates of GABA across the BBB of rats (Krantis, 1984). Even under experimental conditions where GABA permeation rates were increased between 3- to 16-fold [*e.g.*, in young rodents or in Spontaneously Hypertensive Rats], the increased permeation rate was not reflected in increased GABA in the central nervous system (Al-Sarraf, 2002; Al-Awadi *et al.*, 2006). These observations may be explained by studies conducted by Kakee *et al.* (2001) that showed that the efflux rate of GABA though the BBB of rats exceeded influx by approximately 16-fold, and studies indicating that GABA transaminase can rapidly degrade even large doses of intra-cerebrally administered GABA (Kuriyama and Sze, 1971). Slight species differences in BBB permeability of GABA were suggested by van Gelder and Elliott (1958) where GABA entry into the brain may be even more restricted in higher order mammals. In contrast to rodents, where small amounts of GABA have been shown to enter the brain, van Gelder and Elliott (1958) reported that the levels of GABA in the CSF were undetectable 30 minutes following the intravenous administration of high doses of GABA (200 mg/kg body weight) to monkeys.

Animal Toxicity Studies Supporting the Safety of PHARMAGABA

Acute Toxicity Studies

A single-dose, oral toxicity study was conducted by Japan Food Research Laboratories (JFRL, 2002) in 4-week-old male and female Wistar rats (10/sex/group) using a study design based on the Organization for Economic Co-operation and Development (OECD) guidelines for the

testing of chemicals (OECD Guideline 401) (OECD, 1987). The test article used in the study was PHARMAGABA-20 (GABA-20), which was PHARMAGABA (≥80% pure GABA) diluted 4-fold (with dextrose), and therefore had a purity of at least 20% GABA. Animals received a single gavage of GABA-20 dissolved in water to provide a dose of 5,000 mg/kg body weight of PHARMAGABA-20, which would correspond to an acute GABA exposure of 1,000 mg/kg body weight. A control group received equal volumes of water. Standard clinical monitoring and observations of mortality were recorded over a 14-day period. No differences in body weights were observed on Days 7 and 14 for both male and female test animals relative to controls. No evidence of morbidity or incident of mortality was reported, and hence the LD_{50} of GABA-20 in mice was >5,000 mg/kg body weight (or approximately >1,000 mg GABA/kg body weight). Oral LD_{50} values as high as 12 g GABA/kg body weight have been reported in mice (Oshima *et al.*, 1965).

Kato *et al.* (2005) conducted a single-dose toxicity study of a GABA-containing fermented milk in 5-week-old CRj:DC(ICR) mice that were randomized to 1 of 3 treatment groups (number of animals per group not indicated) receiving gavage doses of unfermented milk (skim milk), fermented milk containing 10 mg GABA/100 mL (DGB10), or fermented milk containing 25 mg GABA/100 mL (DGB25). The GABA-containing milk was prepared by fermenting skim milk with *Latobacillus casei* and *Lactococcus lactis*, and the final product was then formulated with added maltitol, pectin, and soy polysaccharide. Oral gavage volumes were 20 mL fluid/kg body weight for each treatment group, such that mice allocated to treatment groups DGB10 and DBG25 received 2 and 5 mg/kg body weight of GABA respectively. Standard endpoints of behavior and growth were monitored over a 14-day period without evidence of toxicity or changes in body weights among the groups.

Subchronic Toxicity Studies

A 28-day toxicity study was conducted by the Japan Scientific Food Association in male and female Wistar rats (Hayami *et al.,* 2005). The test article used in the study was PHARMAGABA-20 (GABA-20), which was diluted PHARMAGABA and identical to the GABA source used in the acute toxicity study of JFRL (2002). Rats (32 days of age) were randomized to 1 of 2 groups (20/sex/group) receiving standard rat chow (control) or feed supplemented with 1% GABA-20 [providing approximately 1,000 mg GABA-20/kg body weight (U.S. FDA, 1993), which would correspond to approximately 200 mg GABA/kg body weight]. Standard clinical monitoring, body weight gain, and food consumption were recorded throughout the course of the experiment. On Day 28, hematological and biochemical tests were performed and standard gross pathology and measurement of organ weights also were conducted. Histopathological testing was performed for brain, heart, liver, kidney, testes, and ovaries. Over the course of the study, no significant differences in weight gain were reported between the treated and control groups, and no differences in average food consumption were observed. No signs of morbidity were observed and no mortality was reported. There were no changes in hematology or biochemical parameters for either male or female treated animals relative to controls; however,

it should be noted that a number of biochemical parameters were below the detection limit of the analytical technique in both control and treatment groups, including alanine aminotransferase (ALT)[2], lactate dehydrogenase (LDH), bilirubin, and cholesterol, indicating potential limitations to the analytical sensitivity and methodology. There were no abnormal findings noted during necropsy The only significant difference in organ weights was absolute and relative testis weights, which were increased from control by 7 and 6% ($p<0.05$), respectively; however, this increase was reported by the authors to be within the range of historical control data. Histopathological investigations also were unremarkable.

Kato *et al.* (2005) conducted a 28-day study in male and female Crj:CD(SD) rats. Following a 1-week acclimatization period, male rats weighing 179.9 to 195.4 g and female rats weighing 145.5 to 163.1 g were randomized to 1 of 3 groups (4/sex/group). The animals were administered, by oral gavage, unfermented milk (skim milk, control), DGB10, or DGB25, which were prepared as per their acute study, with the rats allocated to the DGB10 and DBG25 treatment groups receiving 2 and 5 mg GABA/kg body weight, respectively. The animals were housed under standard animal care conditions, and were permitted *ad libitum* access to feed and water. The animals were observed for signs of toxicity on a daily basis and feed intake, water consumption, and body weights were evaluated once a week. Routine clinical chemistry, hematology, and urinalysis were performed. At the end of the study period, the animals were necropsied, selected organs were weighed, and tissues were preserved for histopathological examination. No significant differences in body weight gain were observed between groups. Other than a slight decrease (<10%; $p<0.05$) in food intake in DGB25 females on Day 11 and decreased (<10%; $p<0.05$) water intake for DGB10 females on Day 4, no significant differences in food or water intakes were noted. With the exception of a slight (2.4%; $p<0.01$) increase in urine specific gravity in DGB25 males, quantitative and qualitative urinalysis was unremarkable among groups. The change observed in urine specific gravity was modest, did not correlate with changes in urine protein or glucose, and was not observed in females, and therefore was considered a spurious finding by the authors. A few sporadic significant changes in hematological parameters (*i.e.*, prothrombin time, mean corpuscular hemoglobin concentration, hematocrit, basophil number, and percent basophil) were noted; however, the changes were modest (<10% for all parameters except basophil number, which decreased from 0.01 to 0.00), in many cases were not dose responsive, and in all cases did not occur in both sexes. Therefore, the various changes were not considered toxicologically relevant. There were no toxicologically relevant changes in serum biochemistry. ALT levels were increased by ~3% in the DGB25 females; however, the effect was not observed in males, and did not correlate with other changes in liver biochemistry parameters. Brain and pituitary weights were increased in the DGB25 males by 4% ($p<0.01$) and 15% ($p<0.05$), respectively, with a 12% ($p<0.05$) increase in pituitary weight relative to body weight. Similar dose-related trends were not observed in females; therefore, the findings of increased brain and pituitary weights were

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[2] Also commonly referred to as glutamate pyruvate transaminase (GPT)

determined by the authors not to be biologically relevant. Finally, microscopic pathology did not reveal any increased incidence of pathological findings in treated animals relative to unfermented milk controls. A no-observed-adverse-effect level (NOAEL) of 5 mg GABA/kg body weight per day, the highest dose tested, can be determined under these study conditions.

Kato *et al.* (2005) also conducted a 90-day sub-chronic toxicity study of the same GABA-containing fermented milk in rats. The experiment was conducted in the same strain of rat, and at 5 weeks of age, the animals were randomized to 1 of 4 groups (4/sex/group). Each animal received 1 of 4 oral gavage treatment regimens: 20 mL of distilled water (control), 20 mL of unfermented milk (negative control), 20 mL of fermented milk containing GABA at a concentration of 10 mg/100 mL (DGB10), or 20 mL of fermented milk containing GABA at a concentration of 25 mg/100 mL (DGB25). Rats allocated to treatment groups DGB10 and DBG25 received 2 and 5 mg GABA/kg body weight, respectively. Animal housing, GABA treatment, and toxicological endpoints were identical to those detailed for the 28-day study. No significant differences in body weight or food and water intake were reported. Quantitative measurements of biochemical and histological urine parameters revealed no compound-related adverse effects. Urine volume was significantly ($p<0.05$) increased by approximately 30 and 45% in the male rats receiving DGB10 and DGB25, respectively. The increase in urine volume was associated with a slight (approximately 1%; $p<0.05$) decrease in urine specific gravity in the DGB25 group. The changes in urine volume and specific gravity did not occur in females. The authors stated that hypotension has been reported to occur with GABA administration, an effect that is often associated with diuretic effects (Shimizu *et al.*, 1959). Since the observed changes in urine volume were not associated with other adverse effects of urine function, and were not observed in females, the observation was reported to be toxicologically insignificant. No abnormalities following ophthalmologic analysis were observed. Hemoglobin concentration was significantly lower in the DGB-treated females relative to the unfermented milk controls; however, the observation was slight (<5%; $p<0.05$) and was not observed in males. In the absence of changes for other indices indicative of anemia, the decrease in hemoglobin observed in females was determined to be toxicologically insignificant. Sporadic decreases ($p<0.05$) in differential leukocyte counts (lymphocyte, neutrophil, and eosinophil) were reported in the DGB25 female animals relative to the unfermented milk group; however, the effects were not dose responsive, were not observed in males, and were not significantly decreased relative to distilled water controls, and therefore, the changes were considered to be a spurious finding and biologically irrelevant. Biochemical indices were unremarkable. Sporadic changes in absolute organ weights were noted with total lung and adrenal weights increased (~10%; $p<0.05$) relative to the unfermented milk controls; however, these changes were not observed in both sexes, were not dose-responsive, and in the case of the adrenals were not significantly changed relative to distilled water controls and hence were considered to be of toxicologically insignificant. Relative pituitary weights were increased in females treated with DGB10 relative to the unfermented milk controls (approximately 20%; $p<0.05$). Again, the observed response was not dose responsive, was not observed in both sexes, was not observed compared to the

distilled water controls, and therefore was considered to be a spurious finding. Macroscopic pathology was unremarkable for all groups. From the results of the toxicity study, a NOAEL of 5 mg/kg body weight, the highest dose tested, could be determined for exposure of Sprague-Dawley rats to GABA-containing fermented milk.

Chronic Studies

In reviewing the application for a tolerance exemption for use of GABA as an ingredient in a pesticide, Auxiogrow WP (comprising a mixture of 36.5% L-glutamic acid and 29.2% GABA), the U.S. EPA stated that it reviewed studies from the "open-literature" that demonstrated that chronic GABA administration at up to 1 g/kg/day in rats and dogs was well tolerated and with no signs of toxicity (U.S. EPA, 1997). The studies supporting this information were not identified during the comprehensive search of the published literature.

Mutagenicity and Genotoxicity Studies

One study was identified in the literature that assessed the potential mutagenicity of GABA-containing fermented milk products, DGB10 and DGB25, which contained GABA at 10 and 25 mg/100 mL, respectively (Osawa *et al.*, 2005). The Rec assay was utilized to assess the potential mutagenicity of GABA milk using *Bacillus subtilis* strains H17 (Rec+) and M45 (Rec-). Doses of DGB25 were added to paper disks at quantities ranging from 46.9 to 750 mg, and for DGB10 at levels ranging from 18.75 to 300 mg. Both studies were conducted in the presence and absence of metabolic activation. There was no evidence of mutagenicity at either concentration of GABA milk.

Studies in Humans

The safety of GABA supplementation has been investigated in a number of studies involving a total of 349 subjects consuming doses of GABA of up to 120 mg for periods of up to 12 weeks. Of these studies, the majority were designed to investigate the potential hypotensive effects of GABA on blood pressure, and approximately 300 hypertensive yet otherwise healthy individuals participated in these studies with no untoward effects reported. Each study included additional safety-related endpoints (*e.g.*, full tabulated summaries of all biochemical, hematological, and urinalysis parameters) and was conducted using healthy subjects. In addition, three human studies also were identified in the literature that indicated that the consumption of high levels of GABA (up to 18 g/day) for a period of up to 4 days was well tolerated, with only minor side effects noted.

Cavagnini *et al.* (1980a,b; 1982) conducted a number of studies in which the oral administration of GABA at doses of 5 g or more in healthy male and female volunteers was investigated. In the first study, 16 females and one male each received a single 5 g oral dose of GABA. The only observations reported by the authors were a slight burning in the throat occasionally accompanied by a sensation of breathlessness soon after administration and lasting a few

minutes (Cavagnini *et al.*, 1980a). Cavagnini *et al.* (1980b) conducted an investigation in which 2 male and 17 female volunteers between 18 and 65 years of age consumed 5 g of GABA dissolved in 150 mL of water. An additional 8 female subjects followed a 4-day regimen of daily GABA consumption, where 18 g of GABA was consumed daily in 4 divided doses, with the last dose being taken 1 hour before a post-treatment insulin tolerance test (test methodology not indicated). The authors reported that GABA consumption was well tolerated with an occasional report of burning in the throat accompanied by a sensation of breathlessness lasting a few minutes. No change in baseline glucose, pulse rate, or blood pressure was observed in association with the consumption of 18 g/day of GABA over a 4-day period. GABA also was observed not to effect glucose concentrations during an insulin tolerance test. In a third study, 12 healthy subjects (3 men and 9 women) each consumed 0 (placebo), 5, or 10 g of GABA dissolved in water on separate days over a 5-day period. Similar to the previous studies, a slight burning sensation in the throat and a sensation of breathlessness lasting a few minutes were reported. In addition, dose-responsive significant ($p<0.01$) increases in immunoreactive insulin and glucagon were observed (60 and 40%, respectively), although the effect was transient and returned to baseline within 180 minutes; however there were no changes in blood glucose levels following GABA consumption (Cavagnini *et al.*, 1982).

Kimura *et al.* (2002) investigated the effect of GABA-containing fermented milk (FGM) on blood pressure and abdominal symptoms in three separate studies involving healthy volunteers. The FGM test material was produced using two strains of lactic acid bacteria (*L. casei* and *L. lactis)* that are capable of converting glutamate to GABA, similar to *L. hilgardii* K3. Following fermentation of the milk, the level of GABA was analyzed and a range of 11.5 to 12.8 mg/ 100 mL was determined. Regular milk was used as the placebo for the second and third tests. The first study was conducted in 8 normotensive men (36.5 ± 9.7 years of age, weighing 75.3 ± 7.6 kg), wherein each subject consumed one 100 mL bottle of FGM (providing approximately 12 mg GABA)/day for 8 weeks. Health interviews were conducted twice during the study, blood clinical chemistry and hematology parameters were measured, and urine samples were assayed for protein, urobilinogen, sugar, and occult blood. The second investigation was a gastrointestinal tolerability study conducted in 12 subjects (6 men and 6 women; 32 ± 6 years of age, weighing 59 ± 8 kg) randomized to 1 of 2 groups, where one group consumed three 100 mL bottles of GABA milk (providing approximately 32 mg GABA/day) and one group consumed an equivalent quantity of regular milk per day within 1 hour after lunch for a period of one week. After one week of treatment, the groups crossed over to the opposite treatment for an additional week. The authors monitored defecation, stool quality, overall health, and gastrointestinal symptoms during the study. The third study was conducted in 16 subjects (8 men and 8 women; 31 ± 4 years of age, weighing 60 ± 11 kg) who were divided into 1 of 2 groups, with 1 group receiving a single supplementation of 300 mL of FGM (providing approximately 32 mg GABA/day) and the other receiving regular milk. Similar safety parameters as measured during the first study were examined. The consumption of GABA (approximately 12 mg/person/day or approximately 0.16 mg/kg body weight/day) for 8 weeks

(Test 1) was well tolerated, and GABA consumption at amounts 3-fold greater (*i.e.*, 32 mg/person/day or approximately 0.63 mg/kg body weight/day) over a course of one week also was well tolerated. The hematological and clinical chemistry data support the safety of the GABA administered. The only significant change noted was a slight decease in serum aspartate aminotransferase (AST) (-17%; $p<0.05$) and chloride (-1.9%; $p<0.05$) levels for subjects consuming GABA. In Test 2, the consumption of GABA did not adversely affect defecation frequency or stool characteristics, and there were no abnormal abdominal signs or symptoms.

Matsubara *et al.* (2002) investigated the tolerability of GABA supplementation in 100 hypertensive yet otherwise healthy adults over an 8-week trial period. A 4-week dose-response pilot study was initially conducted in 51 adults (21 men and 30 women; 20 to 70 years of age, weighing between 50.9 ± 2.8 and 53.1 ± 2.7 kg) randomized to one of 4 groups receiving GABA at oral doses of 0, 20, 40, or 80 mg/day, delivered as one or more tablets containing 20 mg of GABA. The GABA test article used in the study (>99.0% purity) was produced from glutamine using a fermentation refining process. Blood and urine samples were collected at baseline and upon completion of GABA treatment, and standard clinical chemistry and hematology measurements were obtained. Following 4 weeks of GABA supplementation, measurements of safety-related parameters were unremarkable at all doses. The second phase of the study involved 50 male and female subjects, 49 of who were used for a separate tolerability assessment (20 to 70 years of age; number of men and women and weight not provided) and 46 who were used to determine the potential hypotensive effects of GABA (21 men and 25 women; 20 to 70 years of age; weighing between 51.3 ± 1.7 and 52.9 ± 1.8 kg). Subjects were allocated to 1 of 2 groups receiving 4 placebo or GABA tablets per day after breakfast for a period of 8 weeks. Plasma GABA levels were measured throughout the study. The results indicated that orally administered GABA was either poorly absorbed and/or was rapidly cleared since daily intake of 80 mg of GABA/person/day did not alter plasma GABA levels relative to control subjects. Hematological, clinical chemistry, and urinalysis findings were unremarkable. No issues regarding compliance were noted and adverse effect monitoring revealed no GABA-specific adverse effects.

Inoue *et al.* (2003) conducted a randomized, placebo-controlled, single blind trial in 39 mild hypertensive yet otherwise healthy male and female subjects (23 men and 16 women; 28 to 81 years of age, with average weights of 63.5 ± 2.9 and 69.5 ± 4.3 kg for test and placebo groups, respectively) consuming FGM. The test product used in the study was produced from skim milk fermented with *L. casei* and *L. lactis.* The placebo test article was prepared by adding lactic acid to the skim milk. The level of GABA in the FGM was between 10 to 12 mg/100 mL (providing approximately 0.17 mg GABA/kg body weight/day), and no GABA was detected in the placebo preparation. Subjects were randomized to 2 subgroups, one receiving 100 mL of FGM daily at breakfast for 12 weeks, and the other receiving the acidified milk placebo. Subjects were followed for an additional 2-week post-treatment period. Blood samples were taken from each patient at baseline and after the completion of the 12-week treatment period. Standard biochemical, hematological, and urine monitoring was conducted. Two patients in

each group dropped out for reasons that were determined not to be related to the study treatment, and no side effects were reported in either group. Over the 12 weeks of fermented GABA milk consumption, safety endpoint measurements, including heart rate, body weight, hematological and blood chemistry variables, and urine analysis, did not differ between groups.

Watanabe *et al.* (2002) examined the use of a GABA-enriched Brazilian mushroom, *Agaricus blazei Murill* (AG-GABA), in 14 mild hypertensive yet otherwise healthy subjects. The test article was produced by adding the *Agaricus* fruit body to water and allowing it to self-digest (exact meaning is unclear in Japanese translation) for 17 hours at 50°C. The end product contained 2.7% GABA and the freeze-dried powder was added to opaque capsules for use in the study. Each GABA capsule contained 6.25 mg GABA. Placebo capsules were manufactured to contain a similar compositional content without the GABA. A 9-week open-end pilot study was initially conducted in 10 subjects (study subject demographics not provided). Each subject received 25 mg of GABA delivered as 4 capsules/day. The study was initiated following a 1-week non-treatment observation period, and a 6-week post-treatment observation period also was included. Blood serum biochemical samples were taken at Weeks 0 and 9, and a number of biochemical and hematological analyses were performed. Following the pilot study, a double blind comparative crossover test was conducted in subjects consuming AG-GABA over 9 weeks. Fourteen (14) subjects were divided into 2 groups, and following a 1-week pre-treatment observation period, Group A (45.6 ± 12.2 years of age, weighing 73.1 ± 14.8 kg) received AG-GABA and Group B (46.4 ± 15.4 years of age, weighing 69.0 ± 9.3 kg) received placebo. A 1-week washout period was included before the crossover phase. The subjects consumed AG-GABA twice daily (morning and evening) to provide 25 mg GABA/day. Blood and hematological tests were conducted 3 times (during Week 0, 4, and 9), and the evaluated parameters for blood and hematological examinations were identical to the open test. AG-GABA was well tolerated in both studies and serum biochemical/hematological tests did not reveal any significant changes during the open test or crossover studies.

Kajimoto *et al.* (2003a) conducted a placebo-controlled, double blind study investigating the use of FGM (prepared using *L. casei* and *L. lactis*) in 86 healthy subjects with mild or moderate hypertension. The placebo test article was prepared using skim milk powder and was formulated to contain a similar amount of lactic acid as the GABA milk such that both products were indistinguishable in all sensory aspects. The level of GABA in the FGM was equal to or greater than 10 mg/100 mL, and no GABA was detected in the placebo preparation. The subjects were divided into 2 groups, one receiving 100 mL of FGM/day (approximately 10 mg GABA and providing 0.15 mg/kg body weight/day) and the other receiving the placebo beverage. Subjects were instructed to consume the milk every morning for a period of 12 weeks. The following parameters were measured at varying intervals throughout the study period: clinical inspection and interviews, weight and body mass index (BMI), blood pressure and heart rate, urine indices, and standard blood clinical chemistry and hematology. Eight (8) subjects were excluded for failure to meet blood pressure inclusion criteria on the first study day, and 6 subjects dropped out of the trial for private reasons. Over the course of the study,

measurements of body weight and BMI, as well as blood and urine parameters, were unremarkable. A transient decrease in blood pressure was observed in the GABA-treated subjects compared to controls. No GABA-related adverse effects were reported.

In a second randomized, placebo-controlled, double blind trial Kajimoto *et al.* (2003b) assessed the effects of GABA in 108 healthy men and women (42 men and 66 women; 46.4 ± 1.7 and 47.1 ± 1.7 years of age and weighing 62 ± 1.4 and 61.3 ± 1.3 kg in the test and placebo groups, respectively) with high-normal blood pressure. The fermented GABA milk (FGM) was identical to that used by the authors in the previous study (Kajimoto *et al.*, 2003a). No GABA was detected in the placebo milk. The volunteers were divided into 2 groups, with one group consuming 100 mL of FGM (providing approximately 12.3 mg GABA/day) every morning during the 12-week treatment phase, and the other consuming the placebo drink. A 4-week pre-treatment (Weeks -4 and -2) and a 4-week post-treatment (Weeks 14 and 16) observation period also were included in the trial. Weight and BMI were measured. Standard clinical chemistry, hematology, urinalyses and blood pressure monitoring also were conducted at varying time points throughout the study. Following daily GABA administration, no significant compound-related effects on BMI or heart rate were observed, although measurements of blood pressure were significantly decreased compared to controls. Measurements of serum biochemical and hematological parameters were unremarkable and no significant difference in any urinalysis parameters was reported. No GABA-related side effects were observed during the study.

In a third study, Kajimoto *et al.* (2004) investigated the supplemental use of GABA in 88 male and female hypertensive yet otherwise healthy subjects (31 men and 57 women; 53.8 ± 8.5 and 54.7 ± 8.6 years and weighing 59.7 ± 10.1 and 58.8 ± 9.2 kg for test and placebo groups, respectively) using a randomized, double blind, placebo-controlled, parallel group study design. Following a 2-week observation period, subjects were randomized to 1 of 2 groups receiving 4 placebo or GABA tablets (Otsuka Pharmaceutical Co., Japan; 20 mg GABA/tablet) per day before breakfast for a period of 12 weeks, resulting in 0 or 80 mg GABA/day. A 4-week post-treatment observation period also was included in the trial. Blood pressure and body weight were measured in all subjects and blood (clinical chemistry, including plasma GABA levels, and hematology) and urine tests were performed. Similar to Matsubara *et al.* (2002), plasma GABA levels after 12 weeks of consuming GABA at a dose of 80 mg/day were not significantly increased relative to controls. A transient and significant reduction in blood pressure was observed in subjects receiving GABA compared to those in the placebo group. Although some clinical chemistry values were decreased in the GABA group, all values were within historic control ranges and were considered to be clinically irrelevant. Urinalysis findings were considered unremarkable. No GABA-specific adverse effects were reported by any of the subjects and none of the reported symptoms (cold, headache, diarrhea, loose stool passage, hand-foot-mouth disease in one patient, itching, rash) were deemed by the study investigator(s) to be related to GABA administration.

Using a double blind, placebo-controlled, parallel group design, Yamakoshi *et al.* (2006) studied the tolerability of consuming a GABA-enriched food by 177 hypertensive yet otherwise healthy male and female subjects chosen from the untreated subjects' databank of Soiken Inc. The test products included GABA-enriched low-salt soy sauce (120 mg GABA/8 mL), low-salt soy sauce, and regular soy sauce, with a daily intake of 8 mL of soy sauce by all subjects. The GABA levels in the low-salt soy and regular soy sauce products were determined to be <1 mg GABA/ 8 mL. The subjects were randomly allocated to study groups receiving GABA-enriched low-salt soy sauce providing 120 mg GABA/day (48.9 ± 8.9 years of age, weighing 65.9 ± 13.5 kg), low-salt soy sauce (48.1 ± 9.7 years of age, weighing 68.0 ± 14.2 kg), or regular soy sauce (48.9 ± 9.1 years of age, weighing 68.4 ± 13.5 kg). At varying intervals during the study period, blood pressure, heart rate, and body weight were measured, and blood and urine samples were analyzed. After 12 weeks of GABA-enriched soy sauce intake, systolic blood pressure was significantly decreased. There also were some significant changes among the various measured parameters (LDH, albumin, urea nitrogen, and calcium); however, all changes were below 10%, were within the historical reference range, and were deemed by the investigators to be clinically insignificant. The incidence of clinical findings related to adverse effects were similar between groups, and no specific side effect was considered compound-related.

In addition to the animal toxicity studies that were reported to be evaluated by the U.S. EPA in its review of the safety of human exposure to GABA from the use of pesticide, Auxiogrow WP, the agency also made reference to human studies in which daily oral doses of 824 mg GABA/kg body weight were administered for a period of 1 year with no indication of chronic or cumulative toxicity (U.S. EPA, 1997); however, as stated, these studies were not identified during the comprehensive search.

Information Pertaining to the Safety of the Bacterial Enzymes

L. hilgardii K-3, isolated from kimchi (fermented Korean pickles), is a bacterial strain from the *Lactobacillaceae* family of the genus *Lactobacillus* and due to its high glutamate decarboxylase metabolic capacity, is capable of converting large amounts of glutamate to GABA during large scale fermentation. No U.S. federal regulations pertaining to the use of *L. hilgardii* in food were identified; thus, information to support the safe use of *L. hilgardii* K-3 under the intended conditions of use was considered in establishing the safety of PHARMAGABA.

Lactobacillus are Gram-positive, non-spore-forming rods or coccobacilli, and to date, 136 species and 27 subspecies of *Lactobacillus* have been identified (Euzéby, 2007). The bacteria are strictly fermentive organisms and can be aerotolerant or anaerobic, aciduric or acidophilic, and display complex nutritional requirements (*i.e.,* requirements for carbohydrates, amino acids, peptides, fatty acid esters, salts, nucleic acid derivatives, and vitamins) (Bernardeau *et al.*, 2006). Due to their fermentation capabilities, *lactobacilli* have been used to produce a large variety of foods (*e.g.*, beer, wine, cheese, cured meats) for well over a millennium. More

recently, *lactobacilli* have received increased popularity in association with their use as probiotic foods.

In 2000-2001, a workshop that included panel members with expertise in clinical practice, microbiology, intestinal microecology, pathogenicity, nutrition, toxicology, and public health was convened to discuss the safety of *lactobacilli* and *bifidobacteria* used as probiotics in foods and to review criteria for the evaluation of the safety of new probiotics (Borriello *et al.*, 2003). It was the consensus of the expert panel that cases of infection due to *lactobacilli* (and *bifidobacteria*) are rare and increased consumption of probiotic products containing these organisms has not led to increases in these infections in consumers (Borriello *et al.*, 2003). It also is generally accepted that *lactobacilli* and *bifidobacteria* are safe and have a long history of safe consumption (Holzapfel *et al.*, 1998; Vanderhoof and Young, 1998; Saarela *et al.*, 2002; Borriello *et al.*, 2003; Picard *et al.*, 2005; Boyle *et al.*, 2006).

The safety of the *Lactobacillus* genus was extensively evaluated by Bernardeau *et al.* (2006) and the authors stated that "no cases of collective food-borne disease have been reported in healthy people or farm animals following the ingestion of food or feed containing *Lactobacilli*". This view also is supported by Adams (1999), who concluded that based on the long history of consumption, in conjunction with the current available epidemiological, human, and acute animal toxicity data, that lactic acid bacteria commonly occurring in fermented foods and used in probiotics are safe.

The presence of *L. hilgardii* in foods produced by fermentation (*e.g.*, wine, grapes, tibi grains, cheese, and sugar beets) is well established and the organism has a long history of safe consumption (Douglas and Cruess, 1936; Sohier *et al.*, 1999; Baruzzi *et al.*, 2000; Rodas *et al.*, 2005; NCIMB, 2007). In their isolation of bacterial strains from grape musts, Rodas *et al.* (2005) isolated 178 bacterial strains and discovered that the majority (~40%) of *lactobacilli* in wine belong to the *L. hilgardii* species.

The *Lactobacillus* genus is non-pathogenic and non-toxigenic; however, some species of *Lactobacillus*, including *L. hilgardii*, are capable of producing biogenic amines such as tyramine, histamine, putricene, and phenylethylamine. The presence of biogenic amines in wine, cider, cheeses, and cured meats due to the presence of *Lactobacillus* is common but generally does not result in adverse effects or toxicity (Moreno-Arribas *et al.*, 2000; Suzzi and Gardini, 2003; Landete *et al.*, 2005; 2007; Costantini *et al.*, 2006; Ferreira and Pinho, 2006; Garai *et al.*, 2006). Although *L. hilgardii* can produce a variety of biogenic amines, contamination of PHARMAGABA by these compounds in a manner that would be toxicologically relevant is unlikely. A detailed compositional analysis of PHARMAGABA was performed, the results of which indicated that the level of free amino acid contamination is low, and with the exception of glutamic acid, all amino acids are below 0.5%, and many of the biogenic amine precursors (histidine, tyramine, and phenylalanine) were detected at a concentration of ≤0.04%. In addition, PFI has tested

PHARMAGABA for the presence of histamine using HPLC analysis and confirmed that the product contained no detectable levels of histamine.

Another consideration regarding the safety of *L. hilgardii* for use in the production of a food product relates to potential antibiotic resistance of the organism; however, no evidence of antibiotic resistance was noted for any of the 3 *L. hilgardii* strains evaluated by Rojo-Bezares *et al.* (2006) in the presence 12 antibiotics, and it should be noted that this safety concern is likely of limited relevance to the safety of PHARMAGABA, as no bacteria are expected to be present in the final product. Therefore, *L. hilgardii* K-3 is safe for use in the production of PHARMAGABA based on the fact that the particular strain was isolated from food (*i.e.*, kimchi) and the species has a long history of consumption in fermented foods and wine. This conclusion is consistent with the FDA ruling on the GRAS affirmation of a mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis*, wherein the FDA affirmed the GRAS status of the enzyme mixture "... based on published information establishing that *B. licheniformis* is widely recognized as a harmless contaminant found in many foods", which is corroborated by unpublished dietary animal studies of the bacteria-derived enzyme mixture "that confirm(ed) that the food uses of the enzyme product derived from *B. licheniformis* are safe" (U.S. FDA, 1983).

SUMMARY

PFI intends to market a GABA-rich ingredient, PHARMAGABA (>80% purity) as a food ingredient for use at levels of up to 200 mg GABA/serving in various foods, including beverage and beverage bases, ready-to-drink coffee and tea products, chewing gum, and candy and confectionary. PHARMAGABA is consistently manufactured in conformity to appropriate food-grade specifications *via* a fermentation process that utilizes *L. hilgardii* K-3 to catalyze the conversion of L-glutamate to GABA. *L. hilgardii* is a non-pathogenic bacteria species that is present in a number of commonly consumed foods (*e.g.*, cheese, wine, port, and brandy), and although the bacteria is a known producer of biogenic amines, amino acid analysis of PHARMAGABA showed that the level of precursor amino acids used in the production of biogenic amines is ≥0.04% in the final product, and PFI has demonstrated that PHARMAGABA is absent of any detectable histamine.

GABA exists naturally in many different foods and therefore has a long, well-established background of dietary consumption by humans, and the average intake of GABA from its natural occurrence was estimated to be roughly 135.56 mg/person/day. Thus, significant exposure to GABA is expected in association with the consumption of a typical North American diet. On an all-user basis, the total population consumption of GABA under the conditions of intended use was estimated to result in a mean intake of 126.3 mg/person/day (1.97 mg/kg body weight/day) and a 90th percentile intake of 266.4 mg/person/day (4.22 mg/kg body weight/day). The intended use levels are within the range of GABA present in GABA-enriched foods marketed in Japan, which may contain as much as 280 mg of GABA per serving. Moreover, the estimated

intakes are well below the identified recommended intakes of GABA from its inclusion in a number of dietary supplement products. Infants were estimated to have the highest GABA intakes (all-user consumption) relative to body weight (*i.e.*, 4.59 and 14.89 mg/kg body weight for mean and 90th percentile exposures, respectively); however, the PHARMAGABA-containing products will not be marketed for use by infants, and therefore it is expected that the actual exposure to GABA in this group will be minimal.

GABA is a charged molecule with poor bioavailability *via* the oral route (van Gelder and Elliott, 1958), as demonstrated in animal toxicity studies as well as in human studies where the consumption of GABA at doses of 80 mg/person over an 8- to 12-week period did not result in increased plasma GABA levels (Matsubara *et al.*, 2002; Kajimoto *et al.*, 2004). Similar pharmacokinetics exist among various laboratory animal species (*e.g.,* rats, cats, and rabbits) and systemic GABA is rapidly cleared from the blood (*i.e.*, 20-minute half-life in rodents) without evidence of GABA bioaccumulation or retention in any organ pertinent to humans in any of the reviewed studies (van Gelder and Elliott, 1958; Hespe *et al.*, 1969). The liver is the primary metabolic site for GABA (Ferenci *et al.*, 1988), and the catabolism of GABA occurs exclusively *via* GABA transaminase for use as a carbon source in the TCA cycle resulting in CO_2 as the primary waste product (Patel *et al.*, 2005).

The permeation of GABA across the blood-brain barrier is highly limited and not significantly affected by GABA dose (van Gelder and Elliott, 1958; Kuriyama and Sze, 1971; Oldendorf, 1971; Frey and Löscher, 1980; Krantis, 1984; Al-Sarraf, 2002; Al-Awadi *et al.*, 2006), and GABA does not accumulate in the brain following systemic exposure because the efflux rate of GABA across the BBB is greater than its permeation rate and high GABA transaminase activity occurs in the CSF (Kuriyama and Sze, 1971; Kakee *et al.*, 2001). In addition, in their evaluation of the safety of human exposure to GABA, the EPA stated that "GABA does not cross the blood-brain barrier" (U.S. EPA, 2001).

Animal studies indicated that GABA is of low toxicity, and repeat-dose 28- and 90-day toxicity studies conducted with GABA-containing fermented milk demonstrated that exposure to GABA was well tolerated, with NOAEL values of 5 mg GABA/kg body weight/day, the highest dose tested (Kato *et al.*, 2005). Acute toxicity studies conducted with PHARMAGABA resulted in no toxicity in rats consuming 1,000 mg/kg body weight, and 28-day dietary exposure to PHARMAGABA was without adverse effects at a dose of 200 mg/kg body weight/day, the only dose tested. In addition, the EPA has stated that studies it reviewed in the "open-literature" demonstrated that chronic GABA administration at up to 1 g/kg/day in rats and dogs was well tolerated with no signs of toxicity (U.S. EPA, 1997).

Studies involving of GABA in healthy individuals using GABA from pharmaceutical-grade tablets and/or GABA-supplemented food (10 to 120 mg GABA/person/day) for up to 12 weeks in duration indicated that GABA was well tolerated. In addition, short-term oral doses of up to 18 g GABA also were well tolerated in human studies. Daily GABA consumption has been reported

to be associated with reduced blood pressure in hypertensive subjects; however, there was no clear dose-response relationship for this effect, and the maximal effect, although statistically significant in many studies, was modest (*i.e.*, maximum decreases of 5 to 7%) relative to control subjects. In addition, the effect also appeared to be limited to hypertensive individuals, as studies involving normotensive individuals at low (10 mg/person/day for 8 weeks) and high doses (5 to 18 g for 1 to 4 days) did not affect blood pressure (Cavagnini *et al.*, 1980a,b; Kimura *et al.*, 2002). GABA-associated reductions in blood pressure also appeared to be time-dependent and typically required at least 2 weeks before significant reductions were observed. In addition, the EPA referenced clinical studies it reviewed as part of a petition for a tolerance exemption for a GABA-containing pesticide wherein daily oral doses of 824 mg/kg have been administered for a period of 1 year with no indication of chronic or cumulative toxicity (U.S. EPA, 1997).

The safety of the proposed uses of PHARMAGABA is supported by the following facts: PHARMAGABA is manufactured consistent with cGMP using appropriate food-grade materials and the ingredient meets acceptable specifications; GABA occurs naturally in a large variety of foods routinely consumed by the U.S. population at estimated levels of up to 135.6 mg/person/day; GABA has been used in foods in Japan for over 20 years at levels up to 280 mg/50 g serving; GABA does not readily cross the BBB; GABA is metabolized to innocuous substances that are readily cleared from body; GABA occurs naturally in a large variety of foods routinely consumed by the U.S. population at estimated levels of up to 135.6 mg/person/day; and human studies using GABA supplementation failed to identify evidence of adverse health effects following daily GABA intakes up to 18 g for 4 days or following long-term intakes of 120 mg for up to 12 months. The safety of the ingredient is corroborated by the following: an acute and a subchronic toxicity study conducted using PHARMAGABA at doses of 1,000 and 200 mg/kg body weight respectively (the only doses tested) were without evidence of toxicity; a NOAEL of 5 mg/kg body weight/day, the highest dose tested, was established for a fermented GABA milk in rats; and the EPA reviewed toxicity studies in rodents and dogs and concluded that GABA was well tolerated without signs of toxicity at doses up to 1g /kg body weight for a period of up to 1 year.

CONCLUSION

We, the Expert Panel, have, independently and collectively, critically evaluated the data and information summarized above and conclude that the proposed uses of PHARMA GABA, produced consistent with current Good Manufacturing Practice (cGMP) and meeting appropriate food grade specifications, are safe.

We further conclude that the proposed uses of PHARMA GABA are Generally Recognized as Safe (GRAS) based on scientific procedures.

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

25 October 2007

Joseph Borzelleca, Ph.D.
Pharmacology & Toxicology
Medical College of Virginia

Date

29 October 2007

William Waddell, M.D.
Department of Pharmacology and Toxicology
University of Louisville School of Medicine

Date

7 November 2007

Stephen Taylor, Ph.D.
Institute of Agriculture and Natural Resources
University of Nebraska

Date

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Attachment A-1
CV's: Expert Panel

Curriculum Vitae

Joseph F. Borzelleca, Ph.D.

Personal History

Name:	cis Borzelleca	S.S. No:	upon request
Address:		Citizenship:	United States

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Dept. of Pharmacology and Toxicology
Medical College of Virginia
Virginia Commonwealth University
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Educational Background

B.S.	St. Joseph's University, Philadelphia, PA Biology, Chemistry	1952
M.S.	School of Graduate Studies Thomas Jefferson University Jefferson Medical Co llege, Philadelphia, PA Pharmacology, Physiology	1954
Ph.D.	School of Graduate Studies Thomas Jefferson University Jefferson Medical College, Philadelphia, PA Pharmacology, Biochemistry	1956

Academic Appointments

Department of Pharmacology Medical College of Pennsylvania Philadelphia, PA	Instructor-Associate	1956-1959
Department of Pharmacology and Toxicology Medical College of Virginia Richmond, VA 23298-0613	Assistant Professor	1959-1962
	Associate Professor	1962-1967
	Professor	1967-
	Head, Division of Toxicology	1972-1986
	Professor Emeritus	01 July 1996-

Professional Certification

Fellow, Academy of Toxicological Sciences

Professional Affiliations

Societies

Academy of Toxicological Sciences* **
American Association for the Advancement of Science
American Chemical Society
American College of Toxicology*
American Society of Pharmacology and Experimental Therapeutics**
(Environmental Pharmacology Committee; Liaison Committee, SOT; Toxicology Committee)
Institute of Food Technologists (Professional Member)
International Society of Regulatory Toxicology and Pharmacology*
(Member of Council)
Sigma XI
Society of Experimental Biology and Medicine*
(Councilor; Program Chairman of Southeastern Section)
Society for Risk Analysis
Society of Toxicology* **
(Member and/or Chairman: Awards, Education, Legislative Affairs, Membership, Nominating Committees; Secretary of the Society, Councilor, and President; President,
Food Safety Specialty Section)
Virginia Academy of Science*
(Chairman, Medical Sciences Division)

* Held elected office
** Held appointed office or position

Board of Directors

ILSI (until 2002)

Board of Scientific and Policy Advisors

American Council on Science and Health (until 2000)

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Journals

Editor, Food Chemical Toxicology, 1992-

Editorial Board
Environmental Carcinogenesis Reviews, 1981-2000
Journal of Environmental Pathology, Toxicology and Oncology 1977- 2000
Journal of Environmental Science and Health, 1979-2004
Journal of the American College of Toxicology, 1982-
Journal of Toxicology: Cutaneous and Ocular Toxicology, 1982- 1992
Journal of Applied Toxicology, 1989-
Pharmacology, 1978-
Pharmacology and Drug Development, 1980-
Toxicology and Applied Pharmacology, 1975-1978

Consultantships (Past, Present)

Governmental

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

Non-Governmental

National Academy of Sciences - NRC
Committee on Toxicology (Member, Chairman)/Board on Toxicology and Environmental Health Hazards
Safe Drinking Water Committee
Evaluation of Household Substances Committee (1138 Committee)
Food Protection Committee
Food Additives Survey Committee
Committee on Risk-Based Criteria for Non-RCRA Hazardous Wastes
Committee on Risk Assessment of Flame-Retardant Chemicals
Food Chemicals Codex Committee

Federation of American Societies of Experimental Biology
Select Committee on GRAS Substances
Flavors and Extracts
Biotechnology Product Safety
Caprenin GRAS Committee

World Health Organization
Joint Meeting on Pesticide Residues (JMPR) (Member, Chairman)

NATO/CCMS Drinking Water Committee

Industrial

Chemical Companies; Trade Associations

University Activities

Related to Instruction

Prepared a laboratory manual in pharmacology (animal and human studies) (1960)
Introduced the use of closed circuit TV and TV tapes in pharmacology (1960)
Introduced clinical pharmacological experiments into the medical and dental programs (1960)
Planning and participation in continuing education program (Schools of Dentistry, Medicine and Pharmacy)
Planning and administration: each of the three major efforts in pharmacology (dental, medical, pharmacy) since 1960.
Graduate Program - assisted in developing graduate training program in toxicology

Current Teaching Activities

Present lectures on Toxicological Issues, Food Intake and Control

Not Directly Related to Instruction

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

Research

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

Awards

DOD - US Army - Chemical Research Development and Engineering Center
Distinguished Service Award, 1986

National Italian - American Foundation Award
Excellence in Medicine and Community Service, 1987

Thomas Jefferson University
Distinguished Alumnus Award, 1987

Virginia Commonwealth University - School of Basic Health Sciences
Outstanding Faculty Award, 1987

Virginia Commonwealth University, Dept. of Pharmacology and Toxicology
Professor of the Year- 1992

American College of Toxicology
Distinguished Service Award - 1997

Virginia's Life Achievement in Science Award- April 2001

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

International Society for Regulatory Toxicology and Pharmacology's International Achievement Award for 2001- December 2001

Society of Toxicology - Education Award- March 2002

PUBLICATIONS

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

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

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

Borzelleca, J.F.: Drug absorption from the urinary tract of the rat. Nicotine. Arch. Int. Pharmacodyn. Ther. 143: 595, 1963.

Borzelleca, J.F.: Influence of saline and glucose infusions on the course of barbiturate intoxication. Arch. Int. Pharmacodyn. Ther. 146: 163, 1963.

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Borzelleca, J.F.: Drug movement from the isolated urinary bladder of the rabbit. Arch. Int. Pharmacodyn. Ther. 154: 40, 1965.

Borzelleca, J.F.: Rabbit urinary bladder potentials. Invest. Urology 3: 77, 1965.

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Ambrose, A.M., Borzelleca, J.F., Larson, P.S., Smith, R.B., Jr. and Hennigar, G.R.: Toxicologic studies on monochloroacetaldehyde: 2,4-dinitrophenylhydrazone, a foliar fungicide. Toxicol. Appl. Pharmacol. 8: 472, 1966.

Borzelleca, J.F. and Doyle, C.H.: Excretion of drugs in saliva. Salicylate, barbiturate, sulfanilamide. J. Oral. Ther. Pharmacol. 3: 104, 1966.

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Wooles, W.R. and Borzelleca, J F.: Prolongation of barbiturate sleeping time in mice by stimulation of the reticuloendothelial system. J. Reticuloendothel. Soc. 3: 41, 1966.

PUBLICATIONS

Wooles, W.R., Borzelleca, J.F. and Branham, G.W.: The effects of acute and prolonged salicylate administration on liver and plasma triglyceride levels and dietary-induced hypercholesterolemia. Toxicol. Appl. Pharmacol. 10: 1, 1967.

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Kim, K.S., Borzelleca, J F., McKennis, H. and Bowman, E.R.: Pharmacological effects of some nicotine metabolites and related compounds. J. Pharmacol. Exp. Ther. 161: 59, 1968.

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

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

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

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

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

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

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

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

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

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

Iodine in foods: chemical methodology and sources of iodine in the human diet. 1974.

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

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

Evaluation of the health aspects of licorice, glycyrrhiza and ammoniated glycrrhizin as food ingredients. 1974.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evaluation of the health aspects of the tocopherols and a-tocopheryl acetate as food ingredients. 1975.

Evaluation of the health aspects of sorbic acid and its salts as food ingredients. 1975.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evaluation of the health aspects of magnesium salts as food ingredients. 1976.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evaluation of the health aspects of sodium oleate and sodium palmitate as substances migrating to food from paper and paperboard used in food packaging. 1977.

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

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

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

Evaluation of the health aspects of lactic acid and calcium lactate as food ingredients. 1978.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Evaluation of the health aspects of wheat gluten, corn gluten, and zein as food ingredients. 1981.

Evaluation of the health aspects of peptones as food ingredients. 1981.

Evaluation of the health aspects of shellac and shellac wax as food ingredients. 1981.

Evaluation of the health aspects of sodium metasilicate and sodium zinc metasilicate as food ingredients. 1981.

Evaluation of the health aspects of oat gum, okra gum, quince seed gum, and psyllium seed husk gum as food ingredients. 1982.

Contributing Authorship on the Following Publications of the National Academy of Sciences:

Principles and Procedures for Evaluating the Toxicity of Household Substances.
Committee for the Revision of NAS Publication 1138, Committee on Toxicology, Assembly of Life Sciences, National Research Council, National Academy of Sciences
National Academy Press, Washington, D.C. 1977

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

Estimating Consumer Exposure to Food Additives and Monitoring Trends in Use.
Food Additives Survey Committee, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academy Press, Washington, D.C. 1992

Examination of Dietary Recommendations for Salt-Cured, Smoked, and Nitrite-Preserved Foods.
Pariza, M.W., Borzelleca, J.F., Cassens, R.G., Filer, L.J., and Kritchevsky, D.,
CAST Issue Paper Number 8, November 1997

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Professional and Scientific Societies

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member, Executive Committee (1988-91)
member, IFT Expert Panel on Food Safety & Nutrition (1982-88; 1997-present)
member, Program Committee (1985-88)
IFT Scientific Lecturer (1983-86)
Toxicology & Safety Evaluation Division - Chairman (1980-82), Executive Committee (1982-85), Secretary-Treasurer (1985-97)

member, Awards Committee (1991-94)
member, Fellows Award Jury (1988-91)
member, Fellows Committee (1989-92)
Wisconsin section - Chairman (1985-86), Chairman-elect (1984-85), Alternate Councilor (1982-85)
Midwest Food Processing Conference - Executive Committee (1984-87)

American Academy of Allergy, Asthma & Immunology: member, Adverse Reactions to Foods Committee (1981-present)

American Chemical Society: member, Agricultural & Food Chemistry Division

International Association of Food Protection
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American Peanut Research & Education Society

Chair, Food Chemicals Codex Committee, Food and Nutrition Board, National Academy of Sciences (1990-present)
Member, Food and Nutrition Board, National Academy of Sciences (1991-present).
Member, Subcommittee on Upper Reference Levels, Food & Nutrition Board, National Academy of Sciences (1996-present)
Ad Hoc Advisory Committee on Hypersensitivity to Food Constituents- FDA, member (1985-87)
American Council on Science & Health, Board of Scientific Advisors (1986-present)
Editor, Food Science and Technology Series, Academic Press, Inc.
Editor, Advances in Food and Nutrition Research, Academic Press, Inc.
Editorial Board, Journal of Natural Toxins
Editorial Board, Journal of Food Composition and Analysis
Editorial Board, Food and Chemical Toxicology
Section Editor, Food Chemistry and Toxicology, Journal of Food Science
International Food Biotechnology Council, Ad Hoc Committee on Allergenicity of Genetically Engineered Foods (1993-96)
Snack Food Association, Scientific Review Committee (1994-present)
American Gastroenterological Association Foundation, Consensus Conference on E. coli 0157:H7 Infections, panelist (1994)
Member, Board of Directors, Food Allergy Network (1994-02)
Member, Medical Advisory Board, Food Allergy Network (1991-present)
Executive Director, Midwest Advanced Food Manufacturing Alliance (1993-present)
Co-Director, Food Allergy Research & Resource Program, University of Nebraska
Co-Director, Alliance for Food Protection, University of Georgia and University of Nebraska
Board of Directors, Nebraska Industrial Competitiveness Alliance (1994-present)
Board of Directors, Food Update Conference (1994-present)
Program Chairman, Food Update Conference (1998)
Chairman, Food Update Conference (1999)
Chair, FAO/WHO Expert Consultation, Safety of Genetically Modified Foods, Rome (1996)
Member, FAO Expert Consultation, Labeling of Allergenic Foods (1995)
Member, WHO Expert Consultation, Labeling of Allergenic Foods (1999)
Advisory Board, Joint Institute of Food Safety & Applied Nutrition (JIFSPAN), University of Maryland and Food & Drug Administration (1999-present)
Elected, Nebraska Hall of Agricultural Achievement (1999)

PUBLICATIONS

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15. Taylor, S. L., M. Leatherwood, and E. R. Lieber. 1978. Histamine in sauerkraut. J. Food Sci. 43:1030-1032.

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36. Taylor, S. L. 1982. Mutagenesis vs. carcinogenesis. Food Technol. 36:65-68, 98, 100, 102, 103, 127.

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M.D., University of North Carolina, 1955

Fellowships:

Public Health Service Postdoctoral Research Fellow, Department of Pharmacology, University of North Carolina, 1955-1958
National Institutes of Health Special Fellow, Department of Pharmacology, Royal Veterinary College, Stockholm, Sweden, 1965-1966
Scholar, Sloan Foundation, Health Sciences Consortium, 1974-1975

Academic Appointments:

Assistant Professor of Pharmacology, School of Medicine, University of North Carolina, 1958-1962
Associate Professor of Pharmacology, School of Medicine, University of North Carolina, 1962-1972
Associate Professor of Oral Biology, Dental Research Center, University of North Carolina, 1967-1969
Professor of Oral Biology, Dental Research Center, University of North Carolina, 1969-1972
Professor of Pharmacology, College of Medicine, University of Kentucky, 1972-1976
Professor of Oral Biology, College of Dentistry, University of Kentucky, 1972-1976
Adjunct Professor of Pharmacology, School of Medicine, University of Louisville, 1972-1976
Adjunct Professor of Pharmacology, College of Medicine, University of Kentucky, 1977-
Professor of Pharmacology and Toxicology, School of Medicine, University of Louisville, 1977-1998
Emeritus Professor of Pharmacology and Toxicology, School of Medicine, University of Louisville, 1998-
Visiting Professor of Pharmacology and Toxicology, Schools of Medicine and Pharmaceutical Sciences, Showa University, Tokyo, Japan, November 1983-May 1984

Honors:

Centennial Alumnus Distinguished Visiting Professor, School of Medicine, University of North Carolina, February, 1979

Administrative Appointments:

Associate Division Director, Center for Research in Pharmacology and Toxicology, University of North Carolina, 1966-1967
Associate Director, Dental Research Center, University of North Carolina, 1968-1972
Director of Graduate Studies in Pharmacology, University of Kentucky, 1974-1976
Chairman, Department of Pharmacology and Toxicology, University of Louisville, 1977-1997
Emeritus Chairman, Department of Pharmacology and Toxicology, University of Louisville, 1997-

Society Memberships:

American Physiological Society, 1973-
American Society for Pharmacology and Experimental Therapeutics, 1958-
American Teratology Society, 1968-
Association for Medical School Pharmacology, 1977- (Secretary 1986-1988; President 1988-1990)
Sigma Xi, 1958-
Society for Experimental Biology and Medicine, 1956-
Society of Toxicology, 1978-
Ohio Valley Chapter of Society of Toxicology, 1983- (President 1983-84)
Royal Microscopical Society, 1986-
International Society for the Study of Xenobiotics, 1989-
Fellow, Academy of Toxicological Sciences, 1992-

Consultant:

Research Triangle Institute, 1965-1972
Block Drug Company, 1968-1972
Becton, Dickinson and Company, 1971-1972
Baxter-Travenol Laboratories, 1974-1980
Faculty of Medicine, University of Kuwait, 1977-
Baby Products Company, Johnson and Johnson, 1977-1982
Procter and Gamble, 1978-1998
Allied Chemical, 1978-1982
American Cyanamid, 1981-1987
Dow Chemical, 1981-1986
R. J. Reynolds Industries, Inc., Scientific Advisory Board, 1985-1988 (Chairman 1987-1988)
CA Blockers, Inc., 1987-1989
Grain Processing Corporation, Inc., 1988-
Norwich Eaton Pharmaceuticals, Inc., 1988-1998
Distilled Spirits Council of the United States, Inc., 1989-
National Food Processors Association, 1995-1998

Board of Directors:

Computer Assisted Teaching Systems (CATS) Consortium, 1977-1983
Pharmacon Research Foundation, Inc. (Chairman), 1979-

Editorial Board:

Drug Metabolism and Disposition, 1972-1993
Toxicology and Applied Pharmacology, 1981-1989
Human and Experimental Toxicology, 1993-
Toxicologic Pathology, 1997-

University of Kentucky Committees:

College of Medicine Second Year Curriculum (Chairman), 1973-1975
College of Medicine Second Year Promotions, 1973-1975
College of Medicine Educational Policy, 1972-1976
College of Medicine Pharmacy and Therapeutics, 1972-1976
Student Evaluation and Academic Policy for Second Year (Chairman), 1975-1976
Academic Area Advisory Committee for Biological Sciences, 1974-1976 (Chairman, 1975-1976)
Graduate School Fellowships for Biological Sciences, 1974-1976 (Chairman, 1975-1976)
Ad Hoc Committee to Review College of Pharmacy (Chairman), 1976
Ad Hoc Committee to Review Institute of Environmental Sciences, 1976

University of Louisville Committees:

School of Medicine Biomedical Hazards Committee (Chairman), 1977-1983
School of Medicine Institutional Self-Study Task Force for LCME Accreditation (Chairman), 1979-1980
School of Medicine Radiation Safety Committee (Chairman), 1980-1983
Cancer Center Advisory Committee, 1978-1983
Biological Hazards Committee, 1980-1983

Commonwealth of Kentucky Committees:

Kentucky Drug Formulary, 1977-1981
Kentucky Tobacco and Health Institute Technical Advisory Committee, 1977-1983
Kentucky Medical Assistance Program, 1978-1981
Kentucky Heart Association Research Review Committee, 1980-1981

National Committees:

Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals; Fogarty International Center, 1978
Reproductive Effects Assessment Group (Teratology); Environmental Protection Agency, 1980
Educational Affairs Subcommittee of ASPET: New Approaches to Teaching Pharmacology, 1980-1983
ASPET/S0T 1982 Joint meeting in Louisville, Local Committee Chairman
National Committees (cont.):
Educational Affairs Committee of ASPET, Chairman, 1983-1986

Society of Toxicology Committee on Information Handling, 1986-1988
FASEB Education Committee, 1986-1989
Texas Coordinating Board, review of teaching programs, 1983, 1985, 1987, 1990
TLV Committee, American Conference of Governmental Industrial Hygienists, 1995-1998; Chairman, MISCO Subcommittee, 1996-1998.
Chairman, Science Panel, Center for the Study of Environmental Endocrine Effects, 1995-1998.
Epidemiology in Hazard and Risk Assessment: Expert Panel Review of the "London Principles", 1998-1999.
Flavor and Extract Manufacturers' Association of the United States, Expert Panel, 1999-Chairman, 2005-

International Committees:

Alfred Benzon Symposium III, Copenhagen and Lund, Ion Homeostasis of the Brain, May, 1970
International Agency for Research on Cancer, Alcohol Drinking, Lyon, France, October, 1987
International Life Sciences Institute, Ethyl Carbamate, Brussels, Belgium, June, 1989

Invited Lectures:

More than 100 in North America, Europe, Middle East, China, Japan, Korea, Australia, New Zealand, and Thailand

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WILLIAM J. WADDELL

Publications

Butler, T.C. and Waddell, W.J.: A pharmacological comparison of the optical isomers of 5-ethyl-5-phenyl hydantoin (Nirvanol) and of 3-methyl-5-ethyl-5-phenyl hydantoin (Mesantoin). *J. Pharmacol. Expt. Ther.* **110**:120-125, Jan. 1954.

Butler, T.C. and Waddell, W.J.: The role of the liver in the demethylation of N-methyl derivatives of hydantoin and of 2,4-oxazolidinedione. *J. Pharmacol. Expt. Ther.* **110**:241-243, Feb. 1954.

Butler, T.C., Mahaffee, C. and Waddell, W.J.: Phenobarbital: studies of elimination, accumulation, tolerance, and dosage schedules. *J. Pharmacol. Expt. Ther.* **111**:425-435, Aug. 1954.

Butler, T.C. and Waddell, W.J.: A pharmacological comparison of the optical isomers of 5-ethyl-5-methyl-2,4-oxazolidinedione and of 3,5-dimethyl-5-ethyl-2,4-oxazolidinedione (Paramethadione,'Paradione). *J. Pharmacol. Expt. Ther.* **113**:238-240, Feb. 1955.

Waddell, W.J.: Lysis of dog erythrocytes in mildly alkaline isotonic media. *Am. J. Physiol.* **186**:339-342, Aug. 1956.

Waddell, W.J.: A simple ultraviolet spectrophotometric method for the determination of protein. *J. Lab. Clin. Med.* **48**:311-314, Aug. 1956.

Butler, T.C. and Waddell, W.J.: Metabolic conversion of primidone (Mysoline) to phenobarbital. *Proc. Soc. Expt. Biol. Med.* **93**:544-546, Dec. 1956.

Waddell, W.J. and Butler, T.C.: The distribution and excretion of phenobarbital. *J. Clin. Invest.* **36**:1217-1226, Aug. 1957.

Butler, T.C. and Waddell, W.J.: Metabolic deethylation of 5,5-dimethyl-3-ethyl-2,4-oxazolidinedione (Dimedion). *Arch. Int. Pharmacodyn. Ther.* **111**:308-313, Aug. 1957.

Waddell, W.J. and Butler, T.C.: Renal excretion of 5,5-dimethyl-2,4-oxazolidinedione (product of demethylation of trimethadione). *Proc. Soc. Expt. Biol. Med.* **96**:563-565, Dec. 1957.

Butler, T.C. and Waddell, W.J.: N-methylated derivatives of barbituric acid, hydantoin, and oxazolidinedione used in the treatment of epilepsy. *Neurology* **8** (Suppl. l):106-112, April 1958.

Waddell, W.J. and Butler, T. C. : Calculation of intracellular pH from the distribution of 5,5-dimethyl-2,4-oxazolidinedione (DMO). Application to skeletal muscle of the dog. *J. Clin. Invest.* **38**:720-729, May 1959.

Butler, T.C. and Waddell, W.J.: The metabolic fate of 5-ethyl-l-methyl-5-phenyl hydantoin (l-methylnirvanol) and that of 3,5-diethyl-5-phenyl hydantoin (3-ethylnirvanol). *J. Pharmacol. Expt. Ther.* **127**:171-174, Nov. 1959.

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Waddell, W.J. and Hardman, H.F.: Intracellular pH of isolated perfused turtle heart. *Am. J. Physiol.* **199**:1112-1114, Dec. 1960.

Waddell, W.J. and Butler, T.C.: Metabolic demethylation of 1,3-dimethyl-5-ethyl-5-phenyl hydantoin (dimethylnirvanol). *J. Pharmacol. Expt. Ther.* **132**:291-294, June 1961.

Smith, J.A., Waddell, W.J. and Butler, T.C.: Demethylation of N-methyl derivatives of barbituric acid, hydantoin, and 2,4-oxazolidinedione by rat liver microsomes. *Life Sci.* **2**:486-492, July 1963.

Poole, D.T., Butler, T.C. and Waddell, W.J.: Intracellular pH of the Ehrlich ascites tumor cell. *J. Natl. Cancer Inst.* **32**:939-946, April 1964.

Butler, T.C., Poole, D.T. and Waddell, W.J.: 5,5-Dimethyl-2,4-oxazolidinedione-2-C^{14} (DMO-C^{14}) and inulincarboxyl-C^{14} for measurement of intracellular pH. *In*: Roth, L.J. (Ed.): *Isotopes in Experimental Pharmacology.* Chicago, University of Chicago Press, Chapter 17, pp. 205-210, 1965.

Waddell, W.J.: A simple, rapid method for paper chromatography of barbiturates. *Clin. Chem.* **11**:37-39, Jan. 1965.

Chamberlin, H.R., Waddell, W.J. and Butler, T.C.: A study of the product of demethylation of trimethadione in the control of petit mal epilepsy. *Neurology* **15**:449-454, May 1965.

Butler, T.C., Waddell, W.J. and Poole, D.T.: Demethylation of trimethadione and metharbital by rat liver microsomal enzymes: substrate concentration-yield relationships and competition between substrates. *Biochem. Pharmacol.* **14**:937-942, June 1965.

Waddell, W.J.: The metabolic fate of 5-allyl-5-(1-methylbutyl)barbituric acid (secobarbital). *J. Pharmacol. Expt. Ther.* **149**:23-28, July 1965.

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Butler, T.C., Waddell, W.J. and Poole, D.T.: The pH of intracellular water. *Ann. N.Y. Acad. Sci.* **133**:73-77, April 1966.

Butler, T.C., Poole, D.T. and Waddell, W.J.: Acid-labile carbon dioxide in muscle: its nature and relationship to intracellular pH. *Proc. Soc. Expt. Biol. Med.* **125**:972-974, July 1967.

Butler, T.C., Waddell, W.J. and Poole, D.T.: Intracellular pH based on the distribution of weak electrolytes. *Fed. Proc.* **26**:1327-1332, Sept.-0ct. 1967.

Waddell, W.J. and Brinkhous, W.K.: The Ullberg technique of whole-body autoradiography. *J. Biol. Phot. Assoc.* **35**:147-154, Nov. 1967.

Waddell, W.J.: Distribution of urea-^{14}C in pregnant mice studied by whole-body autoradiography. *J. Appl. Physiol.* **24**:828-831, June 1968.

Waddell, W.J., Ullberg, S. and Marlowe, C.: Localization of the bicarbonate and carbonate pools by whole-body autoradiography. *Arch. Int. Physiol. Biochim.* **77**:1-9, Feb. 1969.

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Waddell, W.J. : Intracellular pH. *In*: Siesjo, B.K. and Sorensen, S.C. (Eds.): *Alfred Benzon Symposium III: Ion Homeostasis of the Brain: The regulation of hydrogen and potassium ion concentrations in cerebral intra- and extracellular fluids.* New York, Academic Press, pp. 233-243, 1971.

Mayberry, H.E., Van den Brande, J.L., Van Wyk, J.J. and Waddell, W.J.: Early localization of ^{125}I-labeled human growth hormone in adrenals and other organs of immature hypophysectomized rats. *Endocrinology* **88**:1309-1317, June 1971.

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Waddell, W. J.: The role of carbonic anhydrase in the control of intracellular pH. *In*: Brewer, G.J. (Ed.): *Hemoglobin and Red Cell Structure and Function.* New York, Plenum Press, pp. 215-224, 1972.

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Deak, S.T., Csaky K.G. and Waddell, W.J.: Localization of histochemical correlation of ^{73}AS by whole-body autoradiography in mice. *J. Toxicol. Environ. Health* **1**:981-984, July 1976.

Tucker, A.N. and Waddell, W.J.: Distribution and effect of the weak acids 5,5-dimethyl-2,4-oxazolidinedione (DM0) and 2,4-dinitrophenol (DNP) in membrane vesicles of *micrococcus denitrificans. Arch. Biochem. Biophys.* **176**:21-27, Sept. 1976.

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Waddell, W.J., Marlowe, C., Miripol, J.E. and Garvin, P.J.: The distribution in mice of intravenously administered [^{14}C]di-2-ethylhexyl phthalate determined by whole-body autoradiography. *Toxicol. Appl. Pharmacol.* **39**:339-353, Feb. 1977.

Lyman, G.E. and Waddell, W.J.: Autoradiography of the water compartments in developing teeth of young mice. *Am. J. Physiol.* **232**:F358-F363, April 1977.

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Waddell, W.J. and Marlowe, C.: Inhibition by metyrapone of the accumulation of nicotine-^{14}C in bronchial epithelium of mice. *Arch. Int. Pharmacodyn. Ther.* **234**:294-307, Aug. 1978.

Waddell, W.J. and Marlowe, C.: Cortisone mediated decrease in fetal metabolism of glucose. *Arch. Int. Pharmacodyn. Ther.* **242**:31-34, Nov. 1979.

Waddell, W.J. and Marlowe, C.: Tissue and cellular disposition of paraquat in mice. *Toxicol. Appl. Pharmacol.* **56**:127-140, Oct. 1980.

Waddell, W.J. and Marlowe, C.: Localization of [^{14}C]nitrosonornicotine in tissues of the mouse. *Cancer Res.* **40**:3518-3523, Oct. 1980.

Waddell, W.J. and Marlowe, C.: Biochemical regulation of the accessibility of teratogens to the developing embryo. *In*: Juchau, M.R. (Ed.): *The Biochemical Basis of Chemical Teratogenesis.* New York, Elsevier North-Holland, Chapter 1, pp. 1-62, 1981.

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Keeney, A.H., Waddell, W.J. and Perraut, T.C.: Carcinogenesis and nicotine in malignant melanoma of the choroid. *Tr. Am. Ophth. Soc.* **80**:132-142, 1982.

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Waddell, W.J.: Whole-body autoradiography for development of new products--evaluation of results. *J. Jap. Cosm. Sci. Soc.* **8**:135-142, 1984.

Waddell, W.J., Marlowe, C. and Friedman, M.A.: The distribution of [^{14}C]caprolactam in male, female and pregnant mice. *Food Chem. Toxicol.* **4**:293-303, 1984.

Egashira, T. and Waddell, W.J.: Histochemical localization of monoamine oxidase in whole-body, freeze-dried sections of mice. *Histochem. J.* **16**:919-929, 1984.

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Waddell, W.J., Lech, J.J., Marlowe, C., Kleinow, K.M., and Friedman, M.A.: The distribution of [^{14}C]acrylamide in rainbow trout studied by whole-body autoradiography. *Fundam. Appl. Toxicol.* **14**:84-87, 1990.

Yamamoto, T., Pierce, W.M., Jr., Hurst, H.E., Chen, D., and Waddell, W.J.: Ethyl carbamate metabolism: *in vivo* inhibitors and *in vitro* enzymatic systems. *Drug Metab. Dispos.* **18**:276-280, 1990.

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Kurata, N., Hurst, H.E., Kemper, R.A. and Waddell, W.J.: Studies on induction of metabolism of ethyl carbamate in mice by ethanol. *Drug Metab. Dispos.* **19**:239-240, 1991.

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WILLIAM J. WADDELL

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Appendix B

APPENDIX B

Specifications, Batch Analyses and Additional Compositional Information

Appendix B - Product Analysis

Three manufactured lots of GABA were analyzed to show that the manufacturing process produces a consistent product in terms of its composition. The analytical data for these 3 lots are summarized below in Table B-1. Copies of specifications and certificates of analysis also are included.

Table B-1 Analysis of Manufactured Lots of GABA

Specification Parameter	Specification	Lot Number		
		7B09	6L25	6K22
Appearance	White to light-yellow powder	Conforms	Conforms	Conforms
GABA	>80%	85.2%	88.1%	87.4%
Moisture	<5%	1.9%	1.6%	1.7%
Ash	<15%	3.1%	3.3%	3.5%
Total Heavy Metals (as Pb)	<10 ppm	<10 ppm	<10 ppm	<10 ppm
Lead (ppm)	<0.5 ppm	<D.L.	0.07 ppm	0.15 ppm
Arsenic (ppm)	<2 ppm	<2 ppm	<2 ppm	<2 ppm
Total Aerobic Counts	<1,000 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
Yeast and Mold	<300 CFU/g	<10 CFU/g	<10 CFU/g	<10 CFU/g
Coliform/*Escherichia coli*	Negative	Negative	Negative	Negative

CFU = colony forming units; GABA = *gamma*-aminobutyric acid; Pb = lead; D.L. = Detection limit of 0.05 ppm
See Attachment B-1 for specifications and batch analysis reports. Certificates of analysis for lead are included in Attachment B-2 (presented in Japanese only).

In addition to the batch analyses, compositional analysis for one lot of GABA was conducted. As shown in Table B-1, GABA comprises a minimum of 80% GABA, with lesser amounts of moisture, ash, and lipids, as wells as a small amount of carbohydrates as dietary fiber and saccharides. Sodium chloride accounts for 90% of the total ash and no minerals were present at levels that would be of toxicological concern. A summary of the results of the detailed compositional analysis of GABA is presented in Table B-2.

Table B-2 Detailed Compositional Analysis of GABA

Analysis Parameter	Results (g/100 g)	Method of Analysis[a]
Compositional Parameters		
gamma-Aminobutyric acid	87.9	Amino acid analysis with HPLC
Total amino acids	7.0	Acid hydrolysis with HPLC
Ash	3.4	Direct incineration method
Moisture	1.9	Heated-air drying at normal pressure
Dietary fiber	0.5	Enzyme-weight method
Total saccharide	0.2	Phenol sulfuric acid method
Lipids	≤0.1	Acid decomposition method
Monoglycerides	ND	Gas chromatography
TOTAL	**101**	
Minerals		
Sodium chloride	3.08	Atomic absorption spectrometer method
Sodium	1.21	Atomic absorption spectrometer method
Potassium	0.287	Atomic absorption spectrometer method
Phosphorus	0.0968	ICP method
Calcium	0.0390	ICP method
Magnesium	0.0137	ICP method
Iron	0.00015	ICP method
Zinc	0.00008	ICP method
Manganese	0.00006	ICP method
Copper	ND	ICP method
TOTAL MINERAL CONTENT	**3.52**	

HPLC = high-performance liquid chromatography; ICP = inductively coupled plasma; ND = not detected
Results of compositional analyses are enclosed.

In addition, GABA was subjected to acid hydrolysis and subsequent quantification of the remaining free amino acids. As expected, glutamic acid was the main amino acid identified in GABA, and it was present at 4.7% in the final product. Small amounts of additional amino acids from the fermentation solution also were present, and were generally identified to be at levels below 0.5%. PFI also analyzed the pre-acid hydrolysis total free amino acid and dipeptide content using HPLC, and as presented in Table B-3, 100% of the acid-hydrolyzed amino acid content was accounted for by free amino acids and dipeptides, which indicated that the final product is free of protein contamination.

Table B-3 Detailed Amino Acid Analysis of GABA

Analysis Parameter	Results (g/100 g)[a]		
	Total Amino Acids (Acid Hydrolysis)	Free Amino Acid Content	Polypeptide Content
Arginine	0.02	0.02	ND
Lysine	0.21	0.20	0.01
Histidine	0.04	0.04	ND
Phenylalanine	0.02	0.02	ND
Tyrosine	0.02	0.02	ND
Leucine	0.23	0.23	ND
Isoleucine	0.18	0.16	0.02
Methionine	0.04	0.03	0.01
Valine	0.24	0.24	ND
Alanine	0.42	0.42	ND
Glycine	0.13	0.11	0.02
Proline	0.11	0.11	ND
Glutamic acid	4.70	2.15	2.55
Serine	0.16	0.11	0.05
Threonine	0.14	0.09	0.05
Aspartic acid	0.32	0.17	0.15
Tryptophan	ND	ND	ND
Cysteine	0.02	ND	0.02
TOTAL	**7.00**	**4.12**	**2.88**
Total Amino Acid Content	**7.00**	**7.00**	

ND = not detected
[a] Amino acid and polypeptide analysis was conducted using high-performance liquid chromatography.

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Attachment B-1
Specification + COA

22-Mar-07

Pharma Foods International Co., Ltd
1-49 Goryo-Ohara, Nishikyo-ku,
Kyoto 615-8245, Japan
Phone : +81-75-394-8605
FAX : +81-75-394-8889

SPECIFICATION

Commodity: PHARMA GABA
Shelf Life : 2 years

	Specification	methods
Appearance	white to light yellow powder	Visual appearance
GABA	more than 80%	Amino acid analysis with HPLC
Moisture	less than 5%	Hearted-air drying at normal pressure method (105℃, 5hrs)
Ash	less than 15%	550-600°C, 5hrs (Dry ash method)
Arsenic	less than 2μg/g	DDTC-Ag luminocity absorbance (Method3, Apparatus A)
Heavy Metals	less than 10μg/g	Sodium sulfide colorimetry (Method 2)
Total Aerobic Counts	less than 1000 CFU/g	Methods established by Japan's Specification and Standards for Food Additives (Edited by Japan Food Additives Assosiation, Total Viable Aerobic Count)
Yeast and Mold	less than 300 CFU/g	Methods established by Japan's Specification and Standards for Food Additives (Edited by Japan Food Additives Assosiation, Pour Plate Method)
Coliform / E. coli	negative	Methods established by Japan's Specification and Standards for Food Additives (Edited by Japan Food Additives Assosiation)

Technical Development Dept.

PHARMA FOODS INTERNATIONAL CO.,LTD

Pharma Foods International Co., Ltd
1-49 Goryo-Ohara,Nishikyo-ku,
Kyoto 615-8245 Japan
PHONE : 81-75-394-8605
F A X : 81-75-394-8889

CERTIFICATE OF ANALYSIS

Commodity: PHARMA GABA
Lot. No.: 7B09
Manufacturing Date: 9-Feb-07
Measurement Date: 12-Feb-07
Shelf-Life: 2 years

	Specification	Results
Appearance	white-light yellow powder	conformable
GABA	more than 80%	85.2%
Moisture	less than 5%	1.9%
Ash	less than 15%	3.1%
Arsenic	less than 2μg/g	less than 2μg/g
Heavy Metals	less than 10μg/g	less than 10μg/g
Total Aerobic Counts	less than 1000CFU/g	less than 10CFU/g
Yeast & Mold	less than 300CFU/g	less than 10CFU/g
Coliform / *E. coli*	negative	negative

000136

Technical Development Dept.

Pharma Foods International Co., Ltd
1-49 Goryo-Ohara,Nishikyo-ku,
Kyoto 615-8245 Japan
PHONE : 81-75-394-8605
F A X : 81-75-394-8889

CERTIFICATE OF ANALYSIS

Commodity: PHARMA GABA
Lot. No.: 6L25
Manufacturing Date: 25-Dec-06
Measurement Date: 18-Jan-07
Shelf-Life: 2 years

	Specification	Results
Appearance	white-light yellow powder	conformable
GABA	more than 80%	88.1%
Moisture	less than 5%	1.6%
Ash	less than 15%	3.3%
Arsenic	less than 2μg/g	less than 2μg/g
Heavy Metals	less than 10μg/g	less than 10μg/g
Total Aerobic Counts	less than 1000CFU/g	less than 10CFU/g
Yeast & Mold	less than 300CFU/g	less than 10CFU/g
Coliform / *E. coli*	negative	negative

000137

Technical Development Dept.

PHARMA FOODS INTERNATIONAL CO.,LTD

Pharma Foods International Co., Ltd
1-49 Goryo-Ohara,Nishikyo-ku,
Kyoto 615-8245 Japan
PHONE : 81-75-394-8605
F A X : 81-75-394-8889

CERTIFICATE OF ANALYSIS

Commodity: PHARMA GABA
Lot. No.: 6K22
Manufacturing Date: 22-Nov-06
Measurement Date: 25-Nov-06
Shelf-Life: 2 years

	Specification	Results
Appearance	white-light yellow powder	conformable
GABA	more than 80%	87.4%
Moisture	less than 5%	1.7%
Ash	less than 15%	3.5%
Arsenic	less than 2μg/g	less than 2μg/g
Heavy Metals	less than 10μg/g	less than 10μg/g
Total Aerobic Counts	less than 1000CFU/g	less than 10CFU/g
Yeast & Mold	less than 300CFU/g	less than 10CFU/g
Coliform / *E. coli*	negative	negative

000138

Technical Development Dept.

Attachment B-2
Lead Analysis

Japan Food Research Laboratories

分析試験成績書

第207072092-001号
2007年(平成19年)08月01日

依　頼　者　株式会社　ファーマフーズ

検　体　名　ﾌｧｰﾏｷﾞｬﾊﾞ80
(Lot.7B09)

財団法人
日本食品分析センター
東京本部　〒151-0082　東京都渋谷区笹塚1丁目52番1号
大阪支所　〒564-0051　大阪府吹田市豊津町3番1号
名古屋支所　〒460-0011　名古屋市中区大須4丁目5番13号
九州支所　〒812-0034　福岡市博多区下呉服町1番12号
多摩研究所　〒206-0025　東京都多摩市永山6丁目11番10号
千歳研究所　〒066-0052　北海道千歳市文京2丁目3番
彩都研究所　〒567-0085　大阪府茨木市彩都あさぎ7丁目4番41号

2007年(平成19年)07月26日当センターに提出された上記検体について分析試験した結果は次のとおりです。

分析試験結果

分析試験項目	結果	検出限界	注	方法
鉛	検出せず	0.05 ppm		原子吸光光度法

以　上

本成績書を他に掲載するときは当センターの承認を受けて下さい。

Japan Food Research Laboratories

分析試験成績書

第207090388-001号
2007年(平成19年)09月12日

依　頼　者　株式会社　ファーマフーズ

検　体　名　ﾌｧｰﾏｷﾞｬﾊﾞ 80
Lot.6K22

財団法人
日本食品分析センター
東京本部　〒151-0053　東京都渋谷区代々木町52番1号
大阪支所　〒564-0051　大阪府吹田市豊津町13番1号
名古屋支所　〒460-0011　名古屋市中区大須4丁目5番13号
九州支所　〒812-0044　福岡市博多区千代町1番12号
多摩研究所　〒206-0033　東京都多摩市中沢6丁目11番10号
千歳研究所　〒066-0064　北海道千歳市住吉2丁目8番
彩都研究所　〒567-0085　大阪府茨木市彩都あさぎ7丁目4番41号

2007年(平成19年)09月06日当センターに提出された上記検体について分析試験した結果は次のとおりです。

分析試験結果

分析試験項目	結果	検出限界	注	方法
鉛	0.15 ppm			原子吸光光度法

以　上

本成績書を他に掲載するときは当センターの承認を受けて下さい。

財団法人日本食品分析センター

Japan Food Research Laboratories

分析試験成績書

第207090503-001号
2007年(平成19年)09月13日

依　頼　者　株式会社　ファーマフーズ

検　体　名　ﾌｧｰﾏｷﾞｬﾊﾞ80
Lot. 6L25

財団法人
日本食品分析センター
東京本部　〒151-0053　東京都渋谷区代々木[illegible]木町52番1号
大阪支所　〒564-0051　大阪府吹田市[illegible]3番1号
名古屋支所　〒460-0001　名古屋市[illegible]丁目5番13号
九州支所　〒812-0014　福岡市博多区[illegible]町1番12号
多摩研究所　〒206-0[illegible]　東京都多摩市[illegible]丁目11番10号
千歳研究所　〒066-0[illegible]　北海道千歳市[illegible]京2丁目3番
彩都研究所　〒567-00[illegible]さぎ7丁目4番41号

2007年(平成19年)09月07日当センターに提出された上記検体について分析試験した結果は次のとおりです。

分析試験結果

分析試験項目	結果	検出限界	注	方法
鉛	0.07 ppm			原子吸光光度法

以　上

本成績書を他に掲載するときは当センターの承認を受けて下さい。

財団法人日本食品分析センター

Attachment B-3
Histamine Analysis

Japan Food Research Laboratories

分析試験成績書

第207060355-001号
2007年(平成19年)06月18日

依　頼　者　株式会社　ファーマフーズ

検　体　名　ﾌｧｰﾏｷﾞｬﾊﾞ80
(Lot. 070209A)

財団法人
日本食品分析センター
東京本部　〒151-0053　東京都渋谷区代々木町52番1号
大阪支所　〒564-0051　大阪府吹田市豊津町3番1号
名古屋支所　〒460-0011　名古屋市中区大須3丁目5番13号
九州支所　〒812-0034　福岡市博多区下呉服町1番12号
多摩研究所　〒206-0033　東京都多摩市唐木田4丁目11番10号
千歳研究所　〒066-0064　北海道千歳市文京2丁目3番
彩都研究所　〒567-0085　大阪府茨木市彩都あさぎ7丁目4番41号

2007年(平成19年)06月05日当センターに提出された上記検体について分析試験した結果は次のとおりです。

分析試験結果

分析試験項目	結果	検出限界	注	方法
ﾋｽﾀﾐﾝ	検出せず	0.5 mg/100g		高速液体ｸﾛﾏﾄｸﾞﾗﾌ法

以　上

本成績書を他に掲載するときは当センターの承認を受けて下さい。

財団法人日本食品分析センター

Attachment B-4
Ethyl Carbamate Analysis

Japan Food Research Laboratories

分析試験成績書
Analysis Result Report

第208021242-001号
2008年(平成20年)02月21日
2008 FEB 21

依　頼　者　株式会社　ファーマフーズ
Client　Pharma Foods International CO., Ltd.

検　体　名　Pharma GABA
Sample　(Lot.7B09)

Japan Food Resarch Laboratories
財団法人
日本食品分析センター
東京本部　〒151-0062　東京都渋谷区[illegible]代々木町52番1号
大阪支所　〒564-0051　大阪府吹田市[illegible]町3番1号
名古屋支所　〒460-0011　名古屋市中区大[illegible]4丁目5番13号
九州支所　〒812-0013　福岡市博多区[illegible]県服町1番12号
多摩研究所　〒206-0035　東京都多摩市[illegible]16丁目11番10号
千歳研究所　〒066-0052　北海道千歳市文京2丁目3番
彩都研究所　〒567-0085　大阪府茨木市彩都あさぎ7丁目4番41号

2008年(平成20年)02月15日当センターに提出された上記検体について分析試験した結果は次のとおりです。
The following data is the analysis result of the requested sample (Accepted 2008 FEB 15).

分析試験結果 Analysis Result

分析試験項目 Analysis Item	結果 Result	検出限界 Detection Limit	注	方法 Measuring Method
ｶﾙﾊﾞﾐﾝ酸ｴﾁﾙ(ｳﾚﾀﾝ) Ethyl Carbamate (Urethane)	検出せず Not Detected	0.01 ppm		ｶﾞｽｸﾛﾏﾄｸﾞﾗﾌｰ質量分析法 Gas Chromatograph Mass Spectrometry

以　上

本成績書を他に掲載するときは当センターの承認を受けて下さい。

Appendix C

APPENDIX C

Information Supporting the Stability of GABA

Appendix C - Stability

Bulk Stability of GABA

The stability of GABA stored at room temperature (20°C) for a period of up to 18 weeks was assessed on 3 lots of the ingredient (Lots 7B09, 6L25, and 6K22). Following storage for 11, 17, or 18 weeks each lot of GABA was analyzed for GABA and moisture content in comparison to baseline. As presented in Table C-1, the GABA content of the ingredient remained stable throughout a storage period of up to 18 weeks, and the difference in analytical values were within the deviation of the baseline numbers. Similarly, the analytical values for moisture content of the 3 lots, as presented in Table C-1, indicated that the moisture content remained less than 5%, which is the value established for the product specification. Storage conditions are set as "Keep cool (10°C or less) and in a dry place".

Table C-1 GABA Stability Following Storage at Room Temperature (20°C) for a Period Between 11 and 18 Weeks

Lot Number	Specification (%)	Initial (%)	After stored at 20°C (%)	Difference (%)
7B09	>80	85.2	87.0 (at 11 weeks)	1.8
6L25	>80	88.1	90.1 (at 17 weeks)	2.0
6K22	>80	87.4	87.8 (at 18 weeks)	0.4

Table C-2 Moisture Content of GABA Following Storage at Room Temperature (20°C) for a Period Between 11 and 18 weeks

Lot Number	Specification	Initial (%)	After stored at 20°C (%)	Difference (%)
7B09	<5	1.9	2.0 (at 11 weeks)	0.1
6L25	<5	1.6	1.5 (at 17 weeks)	-0.1
6K22	<5	1.7	1.6 (at 18 weeks)	-0.1

Additional long-term stability studies were conducted on the bulk GABA powder. In these studies the stability of GABA-20 was evaluated. GABA-20 comprises GABA (≥80% purity) diluted 4-fold, and therefore has a purity of at least 20% GABA. GABA-20 was stored for a period of 2 years and 3 months (27 months) at room temperature, and changes in GABA content were measured using HPLC. The GABA content was stable over the test period, and after the 27-month storage period, the GABA content had not changed relative to time 0. The results of this study, although conducted with GABA-20, a diluted form of GABA, indicated that the GABA content of the ingredient was stable for at least 2 years. A summary of the results of the 27-month stability study is presented in Table C-3. Based on the results of the stability testing the shelf-life of GABA was set as 2 years.

Table C-3 Bulk Stability of GABA-20 Powder Following Storage at Room Temperature for a Period of 27 Months

Months	0	6	12	18	24	27
Gamma-Aminobutyric Acid (GABA) (%)	22.1	22.4	22.5	22.1	21.9	22.3

To assess the stability of GABA under heated conditions, GABA powder was maintained at temperatures of 120, 140, or 160°C for a period of 60 minutes. The ingredient demonstrated high GABA stability at 120°C for the 60-minute period, but was considerably reduced at higher temperatures. The stability of GABA powder under these heat conditions is presented in Figure C-1.

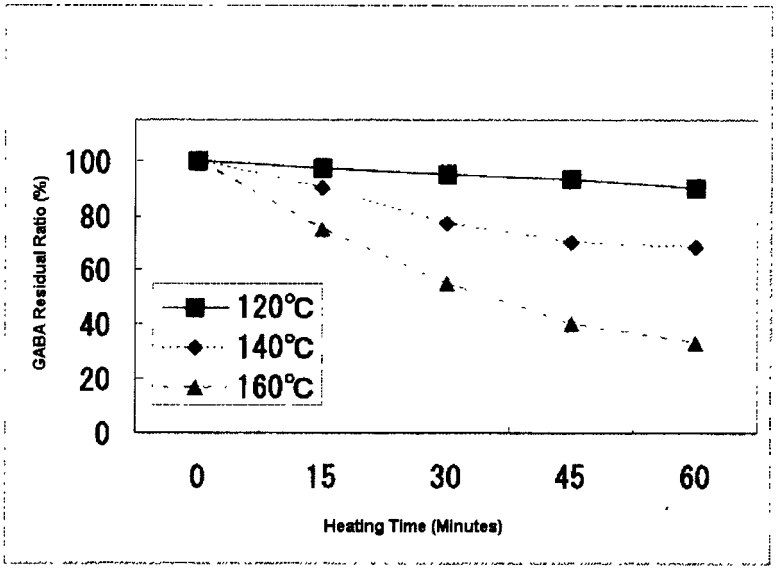

Figure C-1 Bulk Stability of GABA Powder Under Heated Conditions Over a Period of 60 Minutes

Stability of GABA in Solution

When GABA powder was dissolved in solution at a level of 5% and subjected to heated conditions (*i.e.*, temperatures of 100 to 120°C) at neutral pH for a period of 30 minutes, the ingredient showed strong stability. Following a period of 120 minutes, the GABA content of the solution remained stable at a temperature of 100°C, but was slightly reduced at a temperature of 120°C. The stability of a 5% solution of GABA under these conditions is presented in Figure C-2.

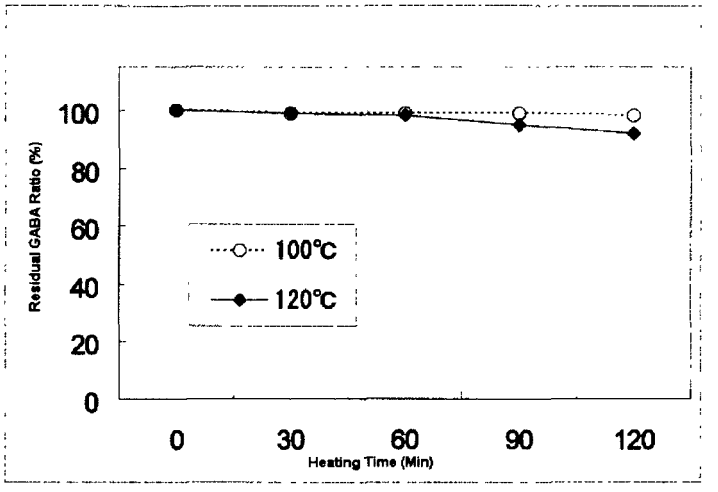

Figure C-2 Stability of a 5% GABA Solution Under Heated Conditions for a Period of 120 Minutes

Additionally, the stability of GABA as 5% solution was assessed under varied pH conditions. GABA was very stable over a pH range of 2 to 6, and stability decreased slightly under alkaline conditions. The stability of a 5% solution of GABA at 100°C under varied pH conditions for 1 hour is presented in Figure C-3.

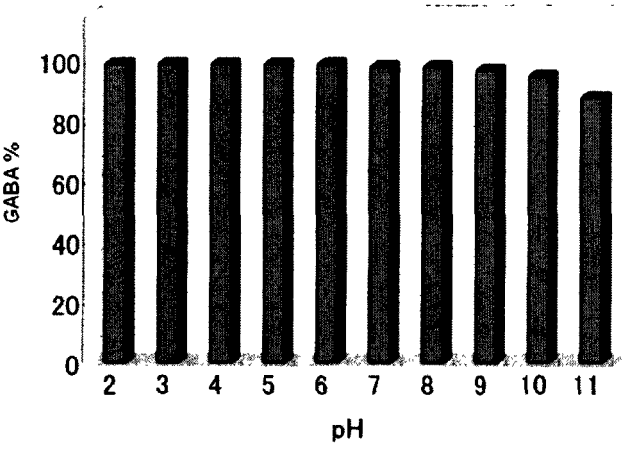

Figure C-3 Stability of a 5% GABA Solution Under Varied pH Conditions

000151

SUBMISSION END

PHARMA FOODS INTERNATIONAL CO.,LTD.
1-49 Goryo-Ohara,Nishikyo-ku,,
Kyoto 615-8245 Japan
PHONE : 81-75-394-8605
F A X : 81-75-394-8889 AM

RECEIVED
DEC 22 2008
BY: (b)(6)

SENT *VIA* FEDEX

December 15, 2008

Robert L. Martin
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD
20740-3835
U.S.A.

Re: Withdrawal of Generally Recognized As Safe (GRAS) Exemption Notice for *gamma*-Amino Butyric Acid (GABA) (GRN 000257)

Dear Dr. Martin,

This letter is to inform you that Pharma Foods International Co., Ltd. would like to withdraw our GRAS Exemption Notice for GABA, which was forwarded to your office on July 16, 2008 and filed as GRN 000257.

Thank you for your kind attention to this matter. Please contact me should you have any questions regarding the withdrawal of this GRAS Exemption Notice.

Sincerely,

(b)(6)

Yusuke SAUCHI, M.Sc
Leader of Research Group 3
Research and Development Dept.
Pharma Foods International Co., Ltd.
y-sauchi@pharmafoods.co.jp

Carlson, Susan

From: Melody Harwood [mharwood@cantox.com]
Sent: Monday, January 05, 2009 2:07 PM
To: Carlson, Susan
Cc: Ryan Simon
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

Hi Dr. Carlson,

Thanks for your follow-up email. Yes, I confirm that Mr. Sauchi is duly authorized by Pharma Foods, Intl. to sign the withdrawal letter. I hope that this response is all that is required for you to acknowledge the withdrawal letter, but if not, please let me know.

Mr. Ryan Simon is working on compiling and re-writing the Notice, so I've copied him on this email. I believe that we are waiting for some data from PFI, and so we will keep you posted on an anticipated timeframe for the call as things progress on our end.

Many thanks again for your kind assistance with this matter.

Best regards,
Melody

-----Original Message-----
From: Carlson, Susan [mailto:Susan.Carlson@fda.hhs.gov]
Sent: Monday, January 05, 2009 1:39 PM
To: Melody Harwood
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

ello Melody,

I hope that you had a Happy New Year. We received the withdrawal letter for the GABA GRAS notice on December 22, 2008. We noticed that the signature on the withdrawal letter is from Yusuke Sauchi while the notice was submitted by Yoshiaki Yoshikuni. We would like to have some assurance from you as Pharma Foods agent that Mr. Sauchi is authorized to sign the withdrawal notice. As I'm sure you can understand, we would hate to send off an acknowledgement of the withdrawal to Dr. Yoshikuni only to find out that he knew nothing of it. If you could just confirm that Mr. Sauchi is duly authorized by Pharma Foods, Intl. by replying to this e-mail, that would be most helpful.

Everyone is pretty much back in the office today, so whenever you are ready to schedule that telecon, please just let me know.

Regards,
Susan

-----Original Message-----
From: Melody Harwood [mailto:mharwood@cantox.com]
Sent: Monday, December 15, 2008 6:46 PM
To: Carlson, Susan
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

Hi Dr. Carlson,

That sounds great, thanks. We sent the withdrawal letter to your offices to the attention of Dr. Martin this afternoon, so you should receive it tomorrow or Wednesday. We envision compiling some of the requested data/answers to your questions and sending a data package for your review before having another call, so please let me know if that would be acceptable. If so, I believe it will take Pharma Foods International Co., Ltd. some time to generate data/translate articles, and they likely wouldn't be able to provide us this information before the end of January, so a call later in the month would be better.

I do plan to take some holidays in January, likely for a 2-week period surrounding the 21st (a destination wedding to go to!), so please let me know if you'd like to discuss the best timing for a call.

Thanks again for your assistance with this matter.

Kind regards,
Melody

-----Original Message-----
From: Carlson, Susan [mailto:Susan.Carlson@fda.hhs.gov]
Sent: Monday, December 15, 2008 2:20 PM
To: Melody Harwood
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

Hello Melody,

I will schedule a teleconference with the review team sometime after the 1st of the year. If you could let me know of some dates that will work for you (or maybe dates that absolutely will not work), that would be helpful. Please be aware, January 19th and January 20th are federal holidays for the DC area (January 19 is for all federal employees, January 20th is only for DC metro area federal employees--they want us off of the roads for inauguration.

Thank you!
Susan

-----Original Message-----
From: Melody Harwood [mailto:mharwood@cantox.com]
Sent: Friday, December 12, 2008 3:56 PM
To: Carlson, Susan
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

Hi Dr. Carlson,

I hope this finds you well. I left you a voice mail in response to your call earlier this week. Our client, Pharma Foods International, will be here on Monday, so we will forward the withdrawal letter with their signature subsequent to our afternoon meeting.

We have been gathering information to try to address the agency's concerns with the Notice, and I am wondering if there is an appropriate avenue to, once the withdrawal letter has been processed, discuss over the telephone the steps we have taken with yourself and your colleagues, as relevant, to get an idea of whether or not we have taken the right approach and if a subsequent Notice would be successful?

I hope that you have a wonderful weekend and I look forward to hearing from you at your earliest convenience.

Kind regards,
Melody

-----Original Message-----
From: Carlson, Susan [mailto:Susan.Carlson@fda.hhs.gov]
Sent: Thursday, November 13, 2008 11:15 AM
To: Melody Harwood
Subject: RE: Cantox:Teleconference: GABA FDA GRAS Notice

Hello Melody,

We had heard about (b) (6) [redacted]. We understand your hesitation to have this elecon today, however we are coming up on the Holiday season and scheduling is becoming challenging. We would like to go ahead and have the meeting today.

Thank you!
Susan