GRAS Notice (GRN) No. 586 http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm ORIGINAL SUBMISSION



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نزخ ند

June 12, 2015

Dr. Paulette Gaynor
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

Dear Dr. Gaynor:

#### Re: GRAS Notification for Taurine

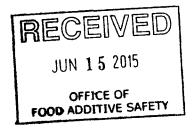
In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized as Safe (GRAS) determination] published in the *Federal Register* [62 FR 18938 (17 April 1997)], I am submitting, in triplicate, as the notifier Intertek Scientific and Regulatory Consultancy, 2233 Argentia Rd, Mississauga, ON, L5N 2X7], a Notice of the determination, on the basis of scientific procedures, that taurine, as defined in the enclosed documents, is GRAS under specific conditions of use as an ingredient in enhanced water beverages, 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 detailed information on the notified substance, a summary of the basis for the GRAS determination, as well as a consensus opinion of an independent panel of experts in support of the safety of taurine under the intended conditions of use, also are enclosed for review by the agency.

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,

(b) (6)

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy



# GRAS Exemption Claim for Taurine for Use in Enhanced Water Beverages

Submitted for:

Office of Food Additive Safety (HFS-200)

Center for Food Safety and Applied

Nutrition (CFSAN)

Food and Drug Administration 5100 Paint Branch Parkway College Park, MD 20740-3835

USA

Submitted by:

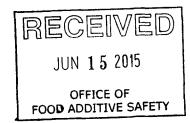
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May 13, 2015



# GRAS Exemption Claim for Taurine for Use in Enhanced Water Beverages

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# GRAS EXEMPTION CLAIM

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

Taurine has been determined to be Generally Recognized as Safe (GRAS) by Intertek Scientific and Regulatory Consultancy for use as an ingredient in enhanced water beverages (*i.e.*, flavored water beverages with other added ingredients such as vitamins and minerals) in the United States (U.S.), 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. Therefore, the use of taurine an ingredient in enhanced water beverages as described below is exempt from the requirement of premarket approval.

Date

Signed,

(b) (6)

MAY 13,2015

#### Ashley Roberts, Ph.D.

Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory

Consultancy

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### I.B Name and Address of Notifier

Intertek Scientific & Regulatory Consultancy 2233 Argentia Road, Suite 201 Mississauga, Ontario, Canada L5N 2X7 www.intertek.com

# I.C Common Name of the Notified Substance

The common name of the notified substance is taurine.

#### I.D Conditions of Intended Use in Food

#### I.D.1 Intended Uses of Taurine and Levels of Use

Taurine is proposed to be marketed as an ingredient in enhanced water beverages. Taurine will be added to enhanced water beverages at concentrations of 45 ppm (*i.e.*, 0.0045%).

# I.D.2 Estimated Consumption of Taurine Based upon Intended Uses

The proposed use of taurine in enhanced water beverages were estimated to result in a mean intake of 15.9 mg/day (0.24 mg/kg body weight/day) and a 90<sup>th</sup> percentile intake of 29.3 mg/day (0.45 mg/kg body weight/day). The individual population group with the highest estimated intakes resulting from the proposed food use was female adults, who displayed mean and 90<sup>th</sup> percentile intakes of 18.7 and 33.3 mg/day (0.26 and 0.45 mg/kg body weight/day, respectively).

When dietary supplements containing taurine were added to the assessment, the mean intake in the total population increased to 24.8 (0.37 mg/kg body weight/day) while the 90<sup>th</sup> percentile level of intake increased to 42.6 mg/day (0.61 mg/kg body weight/day). Within the highest consumers of taurine, (*i.e.*, female adults), inclusion of supplement products in the assessment increased the mean and 90<sup>th</sup> percentile intakes to 29.3 mg/day (0.43 mg/kg body weight/day) and 64.0 mg/day (0.63 mg/kg body weight/day), respectively.

In addition to the consumption of taurine from the proposed food use and supplement products, the contribution of the background diet to the overall intake of taurine should be considered. As detailed in Section 5.1, the background diet is reported to provide up to 400 mg taurine/day. Therefore, the most conservative estimate of the mean and 90<sup>th</sup> percentile all-user intake of taurine from all sources (*i.e.*, enhanced water beverages, taurine-containing supplements, and background diet) would be 424.8 and 442.6 mg/day, respectively, for the total population. Among female adults, the addition of the background dietary intakes to the estimates for the consumption of taurine from the proposed food use and supplement products results in mean and 90<sup>th</sup> percentile intake estimates of 429.3 and 464.0 mg/day, respectively.

The National Health and Nutrition Examination Survey is a short term survey (*i.e.*, 2 days of data per cycle), and can therefore overestimate long-term consumption patterns of products that may be consumed relatively infrequently, such as enhanced water beverages. Estimates derived from these data are therefore considered to represent a worst-case illustration of potential intakes. Additionally, the assessments generated based on the proposed use level for taurine are based on the assumption that all enhanced water beverages consumed contain the maximum indicated quantity of taurine, which also may lead to an overestimation of the impact of the proposed use levels on the consumption of taurine among consumers of these products.

#### I.E Basis for the GRAS Determination

Pursuant to Title 21, Section 170.30 of the Code of Federal Regulations (CFR) (U.S. FDA, 2013a), taurine has been determined to be GRAS on the basis of scientific procedures. This GRAS determination is based on data generally available in the public domain pertaining to the safety of taurine, as discussed herein, and on consensus among a panel of experts who are qualified by scientific training and experience to evaluate the safety of the taurine ingredient as a component of food [see Appendix A, entitled "Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Taurine for Use in Enhanced Water Beverages"].

At the request of Intertek, an Expert Panel of independent scientists, qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether the use of taurine in enhanced water beverages (at levels of 0.0045%) is safe and suitable and would be GRAS based on scientific procedures.

The Panel consisted of the following qualified scientific experts: Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine); Professor I. Glenn Sipes, Ph.D., Fellow AAAS, ATS (University of Arizona); and Professor Gary M. Williams, M.D., DABT, FRCP (New York Medical College).

The Expert Panel, independently and collectively, evaluated the data and information summarized herein and concluded that the intended uses in enhanced water beverages described herein for taurine, meeting appropriate food-grade specifications and manufactured according to current Good Manufacturing Practice (cGMP), are safe, suitable, and GRAS based on scientific procedures. Furthermore, it is the Expert Panel's opinion that other qualified and competent scientists reviewing the same publicly available information would reach the same conclusion.

Taurine is GRAS based on scientific procedures for its intended use in enhanced water beverages. It is therefore excluded from the definition of a food additive, and may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

# I.F Availability of Information

The data and information that serve as the basis for this GRAS Notification 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:

Intertek Scientific & Regulatory Consultancy 2233 Argentia Road, Suite 201 Mississauga, Ontario, Canada L5N 2X7

Should FDA have any questions or additional information requests regarding this notification, Intertek will supply these data and information.

# II. DETAILED INFORMATION ABOUT THE SOURCE AND IDENTITY OF THE SUBSTANCE

# II.A Source and Identity

Molecular formula:

C<sub>2</sub>H<sub>7</sub>NO<sub>3</sub>S

Molecular weight:

125.15 g/mol

Structure:

$$H_2N$$
  $0$   $1$   $S$   $O$   $OH$   $1$   $OH$ 

Physical form:

White crystalline powder

Flavor:

Bitter, sharp flavor; no odor

Melting point:

>300°C

Storage:

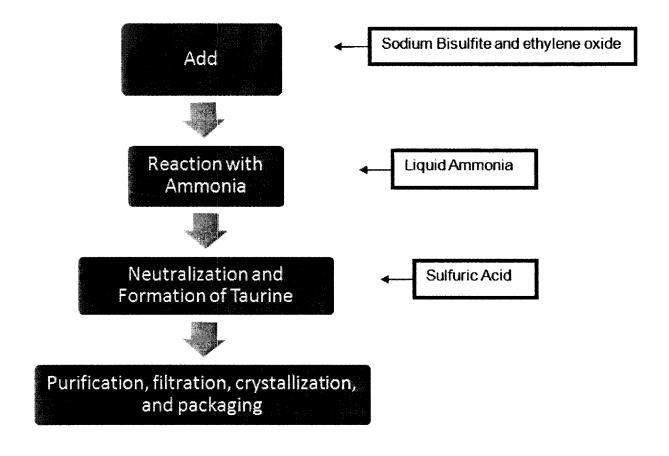
Room temperature

# **II.B** Method of Manufacture

Taurine is produced by Qianjiang Yongan Pharmaceutical Co., Ltd., Fuchi Pharmaceutical Co., Ltd., and Jiangyin Huachang Food Additive Co., Ltd. *via* chemical synthesis (Figure II.B-1).

In the first step of the reaction, sodium bisulfite (added as a starting ingredient, or synthesized from sodium hydroxide and sulfur dioxide) is combined with ethylene oxide, producing isethionic acid (*i.e.*, HOC<sub>2</sub>H<sub>4</sub>SO<sub>3</sub>Na). Liquid ammonia is added to the solution (forming crude aminoethylsodium sulfonate), followed by sulfuric acid (producing crude taurine). The resulting taurine is then purified, filtered, and crystallized, producing a final product that meets the U.S. Pharmacopeia (USP, 2014), Food Chemicals Codex (FCC, 2014), and/or the Japanese Pharmacopeia (15<sup>th</sup> edition – JP, 2006) specifications for taurine (specifications summarized in Section II.C).

Figure II.B-1 General Overview of the Manufacturing Process for Taurine



# **II.C** Specifications and Analytical Data

As indicated above, the taurine produced by the listed manufacturers meets the specifications for taurine established by the USP (2014), the FCC (2014), and/or the JP (15<sup>th</sup> edition). These specifications are presented in Table II.C-1.

Specification Parameter	Specification (USP, 2014)	Specification (FCC, 2014)	Specification (JP, 2006)	
Chemical and Physical				
Characteristics (powder)	NS	White or colorless crystals or white crystalline powder	White or colorless crystals or white crystalline powder	
Assay (anhydrous) (%)	NLT 98.5 and NMT 101.5	98.5 to 101.5	NLT 99.0 and NMT 101.0	
Loss on drying (%)	NMT 0.3	NMT 0.3	NMT 0.2	
Residue on ignition (%)	NMT 0.3	NMT 0.1	NMT 0.1	
Related compounds (%)	NMT 0.5	NMT 0.5 (approx)	NMT 1 spot (not more intense than standard spot)	
pH	NS	NS	4.1 to 5.6	
Chloride (%)	NMT 0.05	NMT 0.01	NMT 0.011	
Sulfate (%)	NMT 0.03	NMT 0.01	NMT 0.010	
Ammonium (%)	NS	NMT 0.02	NMT 0.02	
Heavy Metals				
Heavy Metals (ppm)	NMT 15	NS	NMT 10	
Lead (ppm)	NS	NMT 5	NS	
Iron (ppm)	NMT 30	NMT 10	NMT 10 ppm	
Arsenic (ppm)	NS	NMT 2	NS	
Microbiological				
Total Plate Count (CFU/g)	NMT 1,000	NS	NS	
Yeasts (CFU/g)	NMT 100	NS	NS	
Molds (CFU/g)	NMT 100	NS	NS	
Escherichia coli (in 10 g)	Negative	NS	NS	
Coliforms (in 10 g)	Negative	NS	NS	
Salmonella (in 25 g)	Negative	NS	NS	
Staphylococcus aureus (in 10 g)	Negative	NS	NS	

CFU = colony-forming unit; FCC = Food Chemicals Codex; JP = Japanese Pharmacopoeia; NLT = not less than; NMT = not more than; NS = not specified; USP = United States Pharmacopoeia.

Analysis of sample lots of taurine, as provided by the manufacturers (Qianjiang Yongan Pharmaceutical Co., Ltd., Fuchi Pharmaceutical Co., Ltd., and Jiangyin Huachang Food Additive Co., Ltd.), demonstrates that the manufacturing process as described in Section II.B results in a consistent product compliant with the specifications of the USP (2014), the FCC (2014), and/or the JP (8<sup>th</sup> or 15<sup>th</sup> edition). Certificates of analysis are presented in Appendix B.

# **II.D** Stability

## II.D.1 Bulk Ingredient Stability

The stability of 2 batches of taurine (Lots 20020304 and 0202006, as provided by the manufacturer Qianjiang Yongan Pharmaceutical Co., Ltd.) was evaluated for 10 days under 3 different conditions: 1) under high heat  $(60 \pm 2^{\circ}C)$ ; 2) under relative humidity of 92.5%; and 3) under simulated daylight conditions  $(4,500 \pm 500 \text{ lx illumination})$  (refer to Appendix B for further details). Under all 3 conditions, there were no changes detected with respect to appearance, taurine content, loss on drying, or transmittance, and the samples were determined to be stable.

Four batches of taurine (Lots 20020304, 20020305, 20020306, 0202006; as provided by the manufacturer Qianjiang Yongan Pharmaceutical Co., Ltd.) were evaluated for stability under accelerated storage conditions (*i.e.*,  $40 \pm 2$ °C, relative humidity  $75 \pm 5$ %; for up to 6 months) and long-term storage conditions (*i.e.*,  $25 \pm 2$ °C, relative humidity  $60 \pm 10$ %; for up to 36 months). The results of stability testing under accelerated and long-term storage conditions are presented in Tables II.D.1-1 and II.D.1-2, respectively. Stability data are provided in Appendix B.

#### **XEMPTION CLAIM FOR TAURINE**

# LD.1-1 Accelerated Stability<sup>a</sup>

3)	Manufacturing Lots											
	20020304			20020305		20020306			0202006			
	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	T ti
	99.3	0.12	98.9	99.1	0.10	99.2	99.4	0.10	99.3	99.5	0.14	
	99.2	0.13	99.0	99.0	0.12	99.2	99.2	0.11	99.0	99.4	0.14	
	99.3	0.14	99.0	99.1	0.14	99.0	99.3	0.13	99.2	99.3	0.16	
	99.1	0.16	99.2	99.1	0.15	99.1	99.3	0.14	99.2	99.4	0.17	
	99.3	0.18	99.1	99.2	0.17	99.3	99.1	0.14	99.0	99.2	0.20	Г

maintained under accelerated testing conditions (40  $\pm$  2°C, relative humidity 75  $\pm$  5%) for 6 months.

# I.D.1-2 Long-Term Stability<sup>a</sup>

s)	Manufacturing Lots											_
	20020304			20020305			20020306			0202006		
	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	Transmit- tance (%)	Assay (anhydrous) (%)	Loss on Drying (%)	t
	99.3	0.12	98.9	99.1	0.10	99.2	99.4	0.10	99.3	99.5	0.14	
	99.2	0.13	99.2	99.2	0.11	98.9	99.4	0.11	99.0	99.2	0.15	
er i i	99.2	0.14	99.1	99.1	0.12	99.1	99.2	0.10	99.2	99.4	0.14	
-	99.4	0.15	99.2	99.3	0.14	99.0	99.2	0.12	99.2	99.4	0.16	
	99.0	0.14	98.8	99.2	0.15	98.9	99.1	0.13	99.1	99.1	0.17	
	99.2	0.16	99.1	99.0	0.16	99.0	99.3	0.15	99.0	99.2	0.16	
	99.3	0.14	99.2	99.1	0.14	99.0	99.3	0.16	99.2	99.0	0.18	
	99.1	0.14	99.0	99.0	0.15	99.2	99.0	0.16	99.1	99.1	0.18	

maintained under long term testing conditions (25  $\pm$  2°C, relative humidity 60  $\pm$  10%) for 36 months.

Scientific and Regulatory Consultancy 2015

# III. SELF-LIMITING LEVELS OF USE

The use of taurine will be limited by its sharp, bitter flavor.

# IV. BASIS FOR GRAS DETERMINATION

# IV.A Documentation to Support the Safety of Taurine

The determination that taurine is GRAS is based on scientific procedures, and the information supporting the general recognition of the safety of the ingredient includes:

- The long history of consumption of taurine as a naturally-occurring, conditionally essential component of various foods and human milk.
- Results of pharmacokinetic studies indicating that taurine is metabolically inactive, rapidly absorbed following oral exposure, widely distributed, excreted predominantly unchanged in the urine, and is unlikely to bioaccumulate.
- Results of studies conducted on the ingredient; specifically, an 18-month study in rats [with a determined no-observed-adverse-effect level (NOAEL) of 2,500 mg taurine/kg body weight/day; the highest dose tested], an 8-week study in rats (with a determined NOAEL of 5,000 mg taurine/kg body weight/day; the highest dose tested), and two 13-week studies in rats (with determined NOAELs of 1,000 and 1,656 mg/kg body weight/day).
- Results of several other repeated-dose studies in rats, mice, and guinea pigs;
   reproductive/developmental toxicity studies in mice, rats, and cats; genotoxicity studies;
   and multiple studies in humans.
- Opinions of authoritative bodies, specifically the Scientific Committee on Food (SCF), the European Food Safety Authority (EFSA), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Flavor and Extract Manufacturers' Association of the U.S. (FEMA), and Health Canada, and peer-reviewed expert opinions (Clauson et al., 2008; Shao and Hathcock, 2008).

Moreover, these data were reviewed by a panel of experts, qualified by scientific training and experience to evaluate the safety of ingredients as components of food, who concluded that the intended uses of taurine are safe and suitable and would be GRAS based on scientific procedures [see Appendix A, entitled "Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Taurine for Use in Enhanced Water Beverages"]. A summary of these data is presented herein.

# IV.B Existing Safety Evaluations and Dietary Sources

## IV.B.1 Existing Safety Evaluations

Taurine is used as a nutritive ingredient in energy drinks, dietary supplements, and hypoallergenic soy-based infant formula in the U.S. at levels consistent with cGMP (U.S. FDA, 2013b). However, no U.S. regulations are available pertaining to the direct addition of taurine to food or drinks for humans, although it is permitted as an indirect food additive in paper and paperboard components (21 CFR §176.170; 21 CFR §176.210) (U.S. FDA, 2013c,d).

Taurine has been determined to be GRAS by the Flavor and Extract Manufacturers' Association of the United States (FEMA), for use as a flavoring agent in a number of food categories (*i.e.*, baked goods, meat products, soups, snack foods, breakfast cereals, fats and oils, cheese, poultry, egg products, and fish products), including non-alcoholic beverages at an average maximum use level of 30 ppm [FEMA GRAS 17 (3813) - Smith *et al.*, 1996].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the safety of taurine and established an acceptable daily intake (ADI) of "acceptable", indicating that there is no safety concern at currently estimated levels of intake from use of taurine as a flavoring agent (*i.e.*, 217 µg taurine/day in the U.S.) (JECFA, 2006).

The Scientific Committee on Food (SCF) (SCF, 1999, 2003), considering information available at the time of evaluation, noted that behavioral effects were reported in a 13-week study in rats at doses as low as 300 mg/kg body weight/day (the lowest dose tested by WIL, 2001). The SCF determined margins of safety of 6 to 36 based on estimated human consumption of taurine *via* energy drinks, but noted that further neurotoxicity studies would be required. Since no adverse neurological effects attributable to taurine were reported in a follow-up 13-week study designed specifically to evaluate neurotoxicity in rats (WIL, undated – 42306), a NOAEL of 1,000 mg taurine/kg body weight/day was determined for the original study (WIL, 2001), with a NOAEL of 1,656 mg taurine/kg body weight/day for the subsequent study (WIL, undated; SCF, 2003; EFSA, 2009).

The Scientific Panel on Food Additives and Nutrient Sources of EFSA evaluated the safety of the use of taurine in energy drinks (EFSA, 2009). EFSA considered the results of the two 13-week studies in rats mentioned above (WIL, 2001 and WIL, undated - 42306), and reported NOAELs of 1,000 mg/kg body weight/day for pathological changes and 1,500 mg/kg body weight/day (actual intake 1,656 mg/kg body weight/day) for neurological effects. EFSA (2009) calculated margins of safety of 102 and 43 for mean and 95<sup>th</sup> percentile consumption of taurine from energy drinks only (*i.e.*, 8.3 and 23.3 mg/kg body weight/day, respectively). Given that taurine is endogenous in humans, EFSA concluded that the calculated margins of safety are

sufficiently large to rule out safety concerns with respect to consumption of taurine at the estimated intakes<sup>1</sup> (EFSA, 2009).

In 2012, a scientific opinion on the safety and efficacy of taurine as an additive to feed and water for drinking for all animal species was published by EFSA's Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). The FEEDAP determined an observed safe level (OSL; described as an estimate of safe exposure determined from the highest intake with convincing evidence of safety without the application of additional safety factors) in humans to be 6,000 mg taurine/day (*i.e.*, approximately 100 mg/kg body weight/day for a 60-kg individual) for up to 1 year based on the absence of adverse effects in a large number of studies conducted in adults, children, and infants (EFSA, 2012).

In a guidance document on caffeinated energy drinks sold in Canada, Health Canada established a maximum daily limit of 3,000 mg taurine in caffeinated energy drinks (Health Canada, 2012).

### **IV.B.2 Dietary Sources**

Healthy adults can synthesize taurine from sulfur-containing amino acids (*i.e.*, cysteine and methionine); thus, taurine is considered a conditionally essential nutrient (Clauson *et al.*, 2008). However, in newborn infants and in certain disease states, dietary taurine supplementation may be required to achieve optimal taurine status (Clauson *et al.*, 2008).

Taurine is a natural component of meats and dairy products, and is therefore a component of a typical diet in the U.S. (Laidlaw *et al.*, 1990; Hayes and Trautwein, 1994). Taurine is a component of cow's milk-based infant formulae, and may be added to non-dairy-based infant formulae to compensate for the lack of dairy-derived taurine (Laidlaw *et al.*, 1990). Estimated taurine contents of natural dietary sources are listed in Table IV.B.2-1.

Table IV.B.2-1	Dietary Sources of Taurine				
Food Category		Intakes of Taurine <sup>a</sup>			
Meat and Poultry		11 to 306 mg/100 g wet weight			
Seafood		11 to 827 mg/100 g wet weight			
Dairy Products		2 to 8 mg/100 mL			
Breast Milk and Infant Formula		4 to 7 mg/100 mL			

<sup>&</sup>lt;sup>a</sup> Source: Laidlaw et al., 1990; Hayes and Trautwein, 1994

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<sup>&</sup>lt;sup>1</sup> Consumption of taurine reported to be up to 400 mg/day from dietary sources (*i.e.*, up to 6.7 mg/kg body weight/day for a 60-kg individual), and estimated 95<sup>th</sup> percentile intake from energy drinks only reported to be 1,400 mg taurine/day (*i.e.*, 23.3 mg/kg body weight/day for a 60-kg individual) (EFSA, 2009).

Omnivorous diets have been estimated to provide 9 to 400 mg taurine/day (Rana and Sanders, 1986; Laidlaw *et al.*, 1990). Dietary intake of taurine from a lacto-ovo-vegetarian diet was estimated to be approximately 17 mg/day, while estimates of intake provided by a vegan diet indicate a virtual absence of taurine (Rana and Sanders, 1986; Laidlaw *et al.*, 1990). In individuals with low dietary taurine intake, physiological taurine levels are conserved by enhanced renal taurine reabsorption (further discussion on taurine kinetics provided in Section IV.C) (Hayes and Trautwein, 1994).

#### IV.C Metabolic Fate

Physiological taurine status is determined by dietary intake and from endogenous synthesis. In humans, taurine is considered a conditionally essential nutrient, as it is not synthesized at sufficient levels in newborn infants due to age-dependent expression of cysteine-sulfinic acid decarboxylase, the enzyme predominantly responsible for taurine synthesis in humans (Hayes and Trautwein, 1994). In humans and other mammals, endogenous production of taurine occurs in many tissues, including primarily the liver, brain, and pancreas (EFSA, 2012). As a nutrient, taurine is conjugated with bile acids in the liver, and also is required for cell membrane stabilization, osmoregulation, regulation of calcium flux, neuronal excitability, and may have anti-oxidant functions (Eudy *et al.*, 2013). Taurine is present at concentrations of 2 to 30 mM intracellularly and 35 to 100 μM in extracellular fluids in various mammalian tissues (*e.g.*, plasma, breast milk, and cerebrospinal fluid) (Chesney, 1985; Zelikovic and Chesney, 1989; Trautwein and Hayes, 1990). The total body pool of taurine has been estimated to range from 12 to 18 g (PDRNS, 2008).

Following oral exposure in rodents and humans, taurine is rapidly absorbed *via* a β-amino acid or taurine active transport system in the small intestine (Sved *et al.*, 2007; Ghandforoush-Sattari *et al.*, 2010). In healthy, fasted human volunteers, maximum plasma levels of 0.47 to 0.90 mmol/L were attained within 1 to 2.5 hours following a taurine-rich meal or single oral dose of 4 g taurine (Trautwein and Hayes, 1995). Taurine has a plasma half-life of 0.7 to 1.4 hours, with plasma taurine concentrations in humans reported to return to baseline within 7 hours of consumption (Trautwein and Hayes, 1995; Ghandforoush-Sattari *et al.*, 2010). Taurine is therefore not expected to bioaccumulate, even in individuals consuming unusually large amounts of taurine on a daily basis. This is illustrated by the marginal increases in plasma taurine concentrations reported within 12 to 24 hours of the last dose of taurine in subjects consuming 3 or 6 g taurine/day for 8 weeks or 7 days (respectively) (Zhang *et al.*, 2004a; Rosa *et al.*, 2014). Although these increases (approximately 71 and 97% in the 7-day and 8-week studies, respectively) were statistically significant, they are considered to be physiologically marginal compared to an increase of approximately 933% reported 1 hour after consumption of 4 g taurine in humans (Ghandforoush-Sattari *et al.*, 2010).

As taurine is a polar molecule, it is unable to cross cellular membranes. Tissue concentrations of taurine are under homeostatic control, with cellular uptake mediated by high-affinity, lowcapacity Na<sup>+</sup>/Cl<sup>-</sup> coupled transporters (Sturman et al., 1975). These transporters are saturated at normal plasma taurine concentrations, providing mechanistic support for the observation that tissue concentrations are not appreciably influenced by dietary intake (Sturman, 1973; Trautwein and Hayes, 1995; Sved et al., 2007). Results of studies conducted in Sprague-Dawlev rats administered <sup>14</sup>C taurine orally at doses of 30 or 300 mg/kg body weight/day for up to 14 days indicate that exogenous taurine does not increase total brain taurine concentrations beyond baseline physiological levels (Sved et al., 2007). EFSA (2009) noted that this observation "largely rules out the possibility of stimulatory effects from taurine at the level of the central nervous system". Taurine is distributed to a wide range of tissues, with the highest concentrations observed in the muscle, heart, kidney, and liver; however, only a small quantity of exogenous taurine is exchanged with tissue pools. Radio-label studies in humans demonstrate that taurine is metabolically inert and is not subject to biotransformation events, with the exception of conjugation with bile acids (Sturman et al., 1975). Only a very small proportion of orally administered taurine (i.e., 5%) is incorporated into bile acids, with the majority recovered in the urine (Sturman et al., 1975). Small quantities of putative bacteriaderived sulfated conjugates also have been detected in the urine of humans orally and intravenously administered radiolabeled taurine (Sturman et al., 1975). Overall, the available data demonstrate that approximately 36 to 67% of orally administered taurine is rapidly absorbed from the gastrointestinal tract, following which it may be conjugated with bile acids and excreted through the biliary tract. Unconjugated taurine is widely distributed and rapidly equilibrated, with any excess taurine eliminated primarily via the kidneys.

### IV.D Toxicological Studies

#### **IV.D.1 Acute Studies**

Taurine is of low acute oral toxicity, with median lethal doses ( $LD_{50}$  values) of >1,000 mg/kg body weight in male rats (Doull *et al.*, 1962), >5,000 mg/kg body weight in male and female rats (Kihara *et al.*, 1991), and >7,000 mg/kg body weight in mice (sex not reported; Drugs in Japan, 1990).

#### IV.D.2 Repeated Dose Studies

Takahashi *et al.* (1972a) investigated potential long-term toxicity of taurine in Wistar rats. Nine males and 7 females/group were given diets containing 0, 0.5, or 5% taurine [*i.e.,* providing reported intakes of 0, 250, or 2,500 mg taurine/kg body weight/day, respectively (U.S. FDA, 1993)] for 18 months. The nutritional contents of the test diets were not adjusted to account for the addition of taurine; thus, the high-dose diet contained 95% of the nutrients provided by the control diet. Clinical signs, body weight, and feed consumption were evaluated regularly, and

decedent animals were necropsied and organs were examined histologically. Hematology, organ weights, and histological examinations were conducted upon study termination. Several deaths were reported between Study Months 13 and 18 (i.e., 5, 4, and 3 rats in the control, lowdose, and high-dose groups, respectively). These deaths were attributed to chronic inflammatory diseases of the lung and kidney, and tumors of the mammary gland, which were reported by the study authors to be commonly observed in adult rats of the strain used, and were not attributed to taurine. No compound-related clinical, behavioral, or hematological effects were reported at any dose. There were no significant differences in organ weights between treated and control animals, except for a significant decrease in ovary weight in treated females compared to controls, which may have been due to the reported follicular enlargement observed in control females. No adverse histological effects were observed in the cerebrum, cerebellum, myocardium, spleen, pancreas, gastrointestinal walls, or testes. Moderate dilation of bile capillaries was reported in high-dose males and females, although these effects were not associated with histological evidence of hepatic toxicity, and may have been attributable to increased bile flow. Although the study authors did not report a NOAEL, based on the results presented, a NOAEL of 5% taurine in the diet (2,500 mg/kg body weight/day), the highest dietary concentration tested, could be determined for this study.

Hwang *et al.* (2000) investigated the effects of dietary taurine administration on toxicity associated with oxidized fish oil ingestion in male Wistar rats; however, only results pertaining to animals given control diet (*i.e.*, unsupplemented diet without oxidized fish oil) or control diet supplemented with taurine are presented herein. Rats (6/group) were given diets containing 0 or 5% taurine (*i.e.*, providing approximately 0 or 5,000 mg taurine/kg body weight/day) for 8 weeks. No adverse effects were reported with respect to body weight; plasma aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase; hepatic thiobarbituric acid reactive substances or glutathione; or relative liver or kidney weights.

The subchronic toxicity of taurine also was evaluated in rats (20/sex/group; strain not reported) administered taurine (in water) by gavage at doses of 0, 300, 600, or 1,000 mg/kg body weight/day for 13 weeks (WIL, 2001). This study was conducted in accordance with Organisation for Economic Cooperation and Development (OECD) principles of Good Laboratory Practice (GLP) and in line with OECD guidelines for toxicity testing of chemicals (OECD 408) (OECD, 1998a,b). No deaths or adverse compound-related effects on feed intake or body weight were reported at any dose. Statistically significant differences in hematological and clinical chemistry parameters between treated rats and controls were reported during Study Weeks 4, 8, and 13, although these differences were small and likely not compound-related (no further details reported). A dose-related decrease in urinary pH was observed in treated animals but was attributed to excretion of intact taurine. Small but statistically significant reductions in absolute and relative thyroid and parathyroid gland weights were reported in high-dose males and in all treated females compared to their respective controls. However, these differences were attributed to absolute and relative thyroid and parathyroid gland weights higher

than the historical range in the control group. Although significantly decreased serum thyroid stimulating hormone levels were reported in mid-dose males in Study Week 4, this effect was transient and not dose-related, and therefore not considered to be compound-related. No adverse effects on serum thyroxine levels were reported at any dose. No compound-related gross or microscopic effects were reported in any organs or tissues, including the thyroid at any dose. Dose-dependent increases in motor activity were reported in all treated rats (with greater incidence in females) within 1 hour of dosing. Chewing of forelimbs and hindlimbs was reported in mid- and high-dose males and all treated females, although the statistical significance of this effect was not reported. Following these observations, a functional observational battery (FOB) was conducted on the high-dose and control groups during Study Weeks 6 and 12. Signs of neurostimulation (including greater alertness, cage biting, higher arousal, and hyperresponsiveness) were observed in treated groups (mostly females). However, these effects were observed in single animals (i.e., 1 animal/sex/dose), and their incidence was not significantly different from controls. Impaired rotarod performance was reported in both sexes of the high-dose group, but was not statistically significant due to high variability within groups. Decreased mean ambulatory activity was reported in high-dose males at 6 weeks but not at 12 weeks. The study authors noted that these effects were observed during the first and last months of the 3-month study, indicating a lack of development of tolerance to possible neurological effects of taurine.

In its evaluation of the safety of taurine for use in energy drinks, EFSA (2009) noted that the behavioral effects observed in the study conducted by WIL Research Laboratories Inc. (WIL) (WIL, 2001) were not well described and could be discounted due to the absence of evidence of self-injury. However, EFSA (2009) and the SCF (2003) noted also that the potential for behavioral effects merited further investigation, and that focused neurological studies would be required. Therefore, a GLP- and OECD-compliant neurotoxicity study was conducted in which Crl:CD (SD) rats (20/sex/group) were administered 0, 600, or 1,000 mg taurine/kg body weight/day by gavage (in a deionized water vehicle) for 13 weeks (WIL, undated - 42306). Additional groups of rats (20/sex/group) were given drinking water at target doses of 0, 1,000, or 1,500 mg taurine/kg body weight/day [providing 0, 1,095, or 1,647 mg taurine/kg body weight/day (males) or 0, 1,117, or 1,656 mg taurine/kg body weight/day (females)] for 13 weeks. Based on the results of FOB and locomotor activity tests conducted on all animals prior to study initiation, outliers in locomotor activity were eliminated from the study and animals were randomized according to rotarod test performance. FOB and locomotor activity testing also was conducted during Study Weeks 6 and 12. Body weight and water and feed intake were measured regularly, daily clinical and weekly detailed physical examinations were conducted, and complete necropsies were conducted upon study termination. The study authors noted that taurine was well-tolerated, and reported no treatment-related deaths, adverse effects on body weight or feed consumption, or clinical or macroscopic effects attributable to taurine at any dose. Transient increases in water consumption on Days 0 to 7 were reported in all males provided with taurine in the drinking water (relative to their respective controls), although this

effect was considered an adaptation to the osmotic properties of taurine rather than an adverse effect. No compound-related effects were reported at any dose with respect to locomotor activity testing or FOB parameters (including home cage, handling, open field, sensory, neuromuscular, or physiological observations). EFSA (2009) concluded that the results of this study are sufficient to address the behavioral concerns previously raised, and provide evidence for a NOAEL of 1,000 mg/kg body weight/day in the original toxicity study (*i.e.*, WIL, 2001). A NOAEL of 1,656 mg/kg body weight was determined based on a lack of adverse physiological or behavioral effects following a 13 week exposure *via* drinking water in the follow-up neurological study (WIL, undated – 42306).

Several other studies were identified, in which safety parameters were reported upon consumption of taurine by mice, rats, and guinea pigs. Although these studies were not traditional toxicological studies, safety-related parameters were evaluated (*e.g.*, food intake, body weight, or organ weights). Reduced feed intake, body weight, and urinary excretion of citrate, α-ketoglutarate, and succinate were reported in male rats given drinking water providing up to 7,189 mg taurine/kg body weight/day for 10 weeks (Akira *et al.*, 2013). However, these effects were not associated with pathological changes, and similar adverse effects were not reported in female mice were given diets providing 7,500 mg taurine/kg body weight/day for up to 14 weeks (Fujihira *et al.*, 1970), or in rats given diet providing 5,000 mg taurine/kg body weight/day for 8 weeks (Wang *et al.*, 1997). In the remaining study, no compound-related, physiologically relevant adverse effects were attributed to consumption of drinking water providing 462 mg taurine/kg body weight/day by male guinea pigs for 14 days (Cantafora *et al.*, 1986).

#### IV.D.3 Reproductive and Developmental Toxicity

In the 5 reproductive and developmental toxicity studies evaluated by EFSA (2009) and the SCF (1999, 2003), no evidence of developmental toxicity attributable to taurine was reported upon oral administration of 300 to 4,000 mg taurine/kg body weight/day to pregnant mice or rats during gestation (Takahashi *et al.*, 1972b; Yamada *et al.*, 1981; Friedman *et al.*, 1983). Furthermore, no adverse developmental effects attributable to taurine were reported in a 3-generation study in which mice were continuously administered up to 7.0 g taurine/kg body weight/day (Takahashi *et al.*, 1972b), or in cats administered up to 416 mg taurine/kg body weight/day from 6 months prior to mating until weaning of offspring at 8 weeks of age (Sturman and Messing, 1992).

In an additional recently published study, rats were given control or obesogenic diets (CD or OD, respectively) providing 0 or approximately 1,500 mg taurine/kg body weight/day, from Gestational Day 1 until weaning of offspring at 3 weeks of age (Li *et al.*, 2013). In this study, increased maternal hepatic gene expression related to lipogenesis and inflammation were reported in taurine-treated dams compared to their respective controls, although these changes were not associated with gross or histopathological effects indicative of hepatotoxicity. Li *et al.* 

(2013) reported increased neonatal mortality in pups born to CD dams supplemented with taurine compared to CD controls [i.e.,  $1.4 \pm 0.1\%$  in the CD group compared to  $7.1 \pm 4.0\%$  in the CD-taurine group]. No explanation was given for this observation, but it may have related to the small decrease in maternal body weights of the CD-taurine group relative to CD controls. No comparison to historical data with respect to the range of infant mortality was provided. Thus, the toxicological significance of the reported increase in neonatal mortality is unknown. Adverse effects on offspring mortality were not reported in any of the other identified studies, even upon administration of taurine at higher doses and/or over longer periods of time. In addition, Li *et al.* (2013) reported no significant differences between groups with respect to litter size, pup sex ratio, pup body weight, or any measures of insulin resistance, inflammation, or lipid metabolism. Considering the overall weight of evidence and the SCF (1999, 2003) conclusion that taurine does not demonstrate any potential for teratogenicity, supplemental taurine intake is unlikely to exert adverse effects on reproductive or developmental parameters under the intended conditions of use.

# **IV.D.4 Genotoxicity Studies**

The potential genotoxicity of taurine was evaluated in a series of *in vitro* tests, the results of which are summarized in Table IV.D.4-1. No mutagenic or genotoxic effects were reported in a reverse mutation assay, a *Rec* assay, a chromosomal aberration, or a sister chromatid exchange assay (Laidlaw *et al.*, 1989; Yamada *et al.*, 1993; Cozzi *et al.*, 1995). Taurine's lack of genotoxic potential is corroborated by its long history of use, endogenous nature, natural occurrence in the human diet, and lack of structural alerts for genotoxicity. In addition, the SCF (1999, 2003) concluded that based on the available toxicology studies, taurine does not exhibit any potential for genotoxicity or carcinogenicity.

Table IV.D.4-1 Summary of Mutagenicity and Genotoxicity Studies on Taurine								
Test System	Туре	Concentration	Results	Reference				
Reverse mutation assay	Salmonella typhimurium strains TA98, TA100, TA102	0, 1, 10, or 50 mg/plate	Negative (for mutagenicity and cytotoxicity)	Laidlaw <i>et al.</i> (1989)				
Rec assay	Bacillus subtilis H17 and M45 strains	0.1, 1.0, or 10 mg/disc Use of S9 NR	Negative (for mutagenicity and cytotoxicity)	Yamada et al. (1993)				
In vitro chromosomal aberration and sister chromatid exchange assays	Chinese hamster ovary cells	10 <sup>-3</sup> M Use of S9 NA	Negative (for sister chromatid exchanges and chromosomal aberrations)	Cozzi <i>et al.</i> (1995)				

NA = not applicable; NR = not reported; S9 = metabolic activation; - S9 = without metabolic activation

#### IV.E Studies in Humans

Taurine is often consumed as a component of multi-ingredient energy drinks (often including caffeine and glucuronolactone). The SCF (2003) evaluated the potential for interactions between taurine, caffeine, and glucuronolactone (*i.e.*, all common ingredients in energy drinks), and noted that the 3 ingredients differ widely with respect to their chemical nature. The SCF (2003) reported that a potential for additive interactions between taurine and caffeine may exist, given that the 2 compounds exert stimulatory effects on the central nervous system and diuretic effects on the kidneys. However, the SCF reported that "if there are any cardiovascular interactions between caffeine and taurine, taurine might reduce the cardiovascular effects of caffeine" (SCF, 2003). In a subsequent review in which newer data were considered, EFSA (2009) concluded that the reported stimulatory, diuretic, and natriuretic effects of energy drinks are not likely attributable to taurine. EFSA (2009) reported also that the observed lack of increases from baseline in total brain concentrations of taurine in rats following oral administration of 30 or 300 mg taurine/kg body weight/day for 14 days "largely rules out the possibility of stimulatory effects from taurine at the level of the central nervous system".

In a review of potential safety issues associated with energy drinks, Clauson *et al.* (2008) reported no interactions between taurine and other ingredients in energy drinks, and concluded that "there was insufficient reliable evidence to suggest any adverse events" associated with taurine in such products. Although several human studies in which energy drinks containing taurine were consumed were identified in the literature, the reported effects were not consistent across studies, and the presence of other ingredients in the energy drinks confounded the reported effects. As conclusions regarding the safety of taurine in studies conducted on energy drinks cannot be drawn, these studies will not be discussed herein.

Several human intervention studies that were conducted to assess potentially beneficial effects of consumption of taurine by healthy adults or adults and children with various disease conditions (*i.e.*, hypertension, cystic fibrosis and associated complications, congestive heart failure, cirrhosis, dyskinesias, obesity, renal failure, diabetes, anemia, mixed seizure disorders, myotonic dystrophy, or epilepsy) were identified in the literature. Although the objectives of these studies were not specifically to evaluate safety, endpoints related to safety were reported. Many of these studies, consisting mainly of randomized, double-blind, controlled interventions, were evaluated in a risk assessment conducted by Shao and Hathcock (2008). The study authors concluded that strong evidence supported the safety of taurine at oral doses up to 3 g/day, and that no serious adverse effects were reported in studies in which subjects consumed up to 10 g taurine/day (Shao and Hathcock, 2008). Based on the results presented in these studies, Shao and Hathcock (2008) identified an OSL of 3,000 mg taurine/day. This conclusion was based in part on results of the study by Zhang *et al.* (2004a,b), who reported that consumption of 3,000 mg taurine/day by healthy adults for 7 or 12 weeks was not associated with adverse effects. EFSA (2009) concluded that available data on the

consumption of taurine by humans (including infants, children, and adults) "...do not give any indication of safety concern." and "Such information revealed that oral daily ingestion of taurine doses in the 3-6 g range for periods up to one year, did not produce adverse health effects", and identified an OSL of 6,000 mg/day (EFSA, 2009, 2012).

Among the identified human intervention studies, which include studies summarized by Shao and Hathcock (2008) and EFSA (2009), and those identified in a recent search of the published literature, no adverse effects attributable to taurine were reported in subjects (with normal kidney function) consuming up to 20 g taurine/day for up to 6 weeks, or up to approximately 9 g taurine/day for 7 weeks to 1 year. In 1 study conducted in patients on chronic hemodialysis for renal failure, high doses of taurine (100 mg/kg body weight/day) were associated with vertigo and/or dizziness in 2 of 4 patients tested (Suliman *et al.*, 2002). These symptoms were attributed to the inability of the study subjects to excrete excess taurine, resulting in an accumulation of taurine in the plasma and muscle (as would be expected for any compound eliminated *via* the kidney). Accumulation of taurine is not expected to be of concern in those with normal kidney function.

One case study was identified in which an individual with known sulfite and sulfonamide allergies developed hypersensitivity to taurine (containing a SO<sub>3</sub> moiety) above a threshold level (estimated to be approximately 250 to 300 mg taurine) (Stohs and Miller, 2014). Challenge tests provided evidence for hypersensitivity to taurine. Although this individual had demonstrated allergies to a variety of substances, this is the first case reporting hypersensitivity to taurine.

#### IV.G Summary and Basis for GRAS Conclusion

The GRAS determination for the use of taurine as a food ingredient is based on scientific procedures. Taurine is a conditionally essential, non-protein aminosulfonic acid that is synthesized endogenously in mammals, and is consumed in a typical omnivorous diet at levels up to 400 mg/day. The safety of taurine under the intended conditions of use in enhanced water beverages at levels of up to 0.0045% is supported by the long history of consumption of supplementary and naturally-occurring dietary taurine (*i.e.*, at doses of 3 to >6 g/day), and the results of animal and human studies as described above.

The proposed use of taurine in enhanced water beverages were estimated to result in a mean intake of 15.9 mg/day (0.24 mg/kg body weight/day) and a 90<sup>th</sup> percentile intake of 29.3 mg/day (0.45 mg/kg body weight/day). The individual population group with the highest estimated intakes resulting from the proposed food use was female adults, who displayed mean and 90<sup>th</sup> percentile intakes of 18.7 and 33.3 mg/day (0.26 and 0.45 mg/kg body weight/day, respectively).

When dietary supplements containing taurine were added to the assessment, the mean intake in the total population increased to 24.8 (0.37 mg/kg body weight/day) while the 90<sup>th</sup> percentile

level of intake increased to 42.6 mg/day (0.61 mg/kg body weight/day). Within the highest consumers of taurine, (*i.e.*, female adults), inclusion of supplement products in the assessment increased the mean and 90<sup>th</sup> percentile intakes to 29.3 mg/day (0.43 mg/kg body weight/day) and 64.0 mg/day (0.63 mg/kg body weight/day), respectively.

In addition to the consumption of taurine from the proposed food use and supplement products, the contribution of the background diet to the overall intake of taurine should be considered. As detailed in Section 5.1, the background diet is reported to provide up to 400 mg taurine/day. Therefore, the most conservative estimate of the mean and 90<sup>th</sup> percentile all-user intake of taurine from all sources (*i.e.*, enhanced water beverages, taurine-containing supplements, and background diet) would be 424.8 and 442.6 mg/day, respectively, for the total population. Among female adults, the addition of the background dietary intakes to the estimates for the consumption of taurine from the proposed food use and supplement products results in mean and 90<sup>th</sup> percentile intake estimates of 429.3 and 464.0 mg/day, respectively. As detailed above, these intake estimates likely overestimate long-term consumption patterns, are based on the assumption that the enhanced water beverages consumed contain the maximum indicated quantity of taurine, and are therefore considered to represent a worst-case illustration of potential intakes.

Results of studies in humans and rats indicate that taurine is widely distributed following rapid absorption from the gastrointestinal tract. Taurine concentrations in various tissues (including the brain) are under homeostatic control, and excess taurine is eliminated by the kidneys in a dose-dependent manner. Since Na<sup>+</sup>/Cl<sup>-</sup>-coupled taurine transporters are saturated at physiological plasma taurine concentrations, tissue concentrations are not substantially affected by dietary intake of taurine. Taurine is excreted predominantly unchanged in the urine, with minimal excretion as urinary sulfate or fecal bile salts. Unabsorbed taurine may be broken down by intestinal bacteria to sulfate, or to carbon dioxide, water, and ammonia. Marginal increases in fasting plasma taurine concentrations reported in human subjects following consumption of 3 or 6 g taurine/day for 8 weeks or 7 days (respectively; compared to an approximately 9- to 13-fold greater increase reported within 1 hour of taurine consumption) indicate that excess taurine is efficiently eliminated in healthy subjects, and is unlikely to bioaccumulate. Due to the short half-life of taurine, its efficient excretion by the kidneys, and the inability of exogenous taurine to influence tissue concentrations, the likelihood that taurine will influence normal physiological processes is limited.

Taurine is of low acute oral toxicity, with LD<sub>50</sub> values of >1,000 to >7,000 mg/kg body weight reported in rats and mice. An oral NOAEL of 2,500 mg/kg body weight/day was determined based on a lack of adverse effects reported in an 18-month study in which male and female rats were given diets providing up to 2,500 mg taurine/kg body weight/day (Takahashi *et al.*, 1972a). This NOAEL is supported by a NOAEL of 5,000 mg/kg body weight/day, reported in male rats following 8 weeks of dietary administration (Hwang *et al.*, 2000), and also by NOAELs of 1,000

and 1,656 mg/kg body weight/day, reported by EFSA (2009) and the SCF (1999, 2003) based on a lack of adverse pathological or neurological effects (respectively) reported in 2 unpublished 13-week oral studies in rats (WIL, 2001; WIL, undated – 42306). No clear evidence of reproductive or developmental toxicity attributable to taurine at doses up to 6.42 g/kg body weight/day was reported in the identified studies in mice, rats, or cats. Results of genotoxicity assays are consistently negative, and the SCF (1999, 2003) concluded that the available toxicological studies did not indicate any potential for genotoxicity, teratogenicity, or carcinogenicity.

The SCF (2003) reported that a potential for additive interactions between taurine and caffeine may exist, given that the 2 compounds have been reported to exert stimulatory effects on the central nervous system and diuretic effects on the kidneys. However, the SCF (2003) reported also that taurine might mitigate the cardiovascular effects of caffeine. EFSA (2009) concluded that the reported stimulatory, diuretic, and natriuretic effects of energy drinks are not likely attributable to taurine, and that a lack of increased brain taurine concentrations in a 14-day rat study "largely rules out the possibility of stimulatory effects from taurine at the level of the central nervous system".

Comprehensive reviews of the published literature characterizing the consumption of taurine by humans (including studies conducted in healthy adults, and adults and children with various health conditions) have been conducted (SCF, 2003; Shao and Hathcock, 2008; EFSA, 2009). Based on the available human data, Shao and Hathcock (2008) determined an OSL of 3,000 mg taurine/day. Using the identified NOAELs of 1,000 and 1,500² mg taurine/kg body weight/day [determined based on the results of the 13-week studies conducted by WIL (2001, undated)], EFSA (2009) calculated margins of safety of 102 and 43 for mean and 95<sup>th</sup> percentile consumption of taurine from energy drinks only (*i.e.*, 8.3 and 23.3 mg/kg body weight/day, respectively, for a 60-kg individual). Given that taurine is endogenous in humans, EFSA (2009) concluded that the calculated margins of safety are sufficiently large to rule out safety concerns with respect to consumption of taurine at estimated intakes from energy drinks.

Among the human studies identified, no adverse effects attributable to taurine were reported in subjects (with normal kidney function) consuming up to 20 g taurine/day for up to 6 weeks, or up to approximately 9 g taurine/day for 7 weeks to 1 year. In 1 study conducted in patients on chronic hemodialysis for renal failure, high doses of taurine (100 mg/kg body weight/day) were associated with vertigo and/or dizziness. These symptoms were attributed to accumulation of taurine in the systemic circulation and muscle tissue (due to the inability of the study subjects to excrete excess taurine *via* the kidneys), and are not expected to occur in those with normal kidney function. One case of hypersensitivity to taurine above a threshold level (estimated to be approximately 250 to 300 mg taurine) was identified; although this individual had demonstrated

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<sup>&</sup>lt;sup>2</sup> Actual calculated dose of 1,656 mg/kg body weight/day (WIL, undated – 42306).

allergies to a variety of substances, this is the only reported case to date of taurine hypersensitivity (Stohs and Miller, 2014).

Together, the information provided above supports the conclusion that the consumption of taurine under the proposed conditions of use would not be expected to produce adverse effects in consumers. Finally, the Expert Panel convened on behalf of Intertek and, independently and collectively, evaluated the data and information summarized above and concluded that the proposed use of taurine, produced in accordance with cGMP and meeting appropriate foodgrade specifications, is safe and suitable. Furthermore, the Expert Panel unanimously concluded that the proposed use of taurine is GRAS based on scientific procedures. It is also the Expert Panel's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. Therefore, Intertek has concluded that taurine is GRAS under the proposed conditions of use on the basis of scientific procedures. As such, the ingredient is excluded from the definition of a food additive and thus may be marketed and sold for the uses designated above in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

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# Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Taurine for Use in Enhanced Water Beverages

# August 15, 2014

At the request of Intertek Scientific and Regulatory Consultancy (Intertek), an Expert Panel of independent scientists, qualified by their scientific training and relevant national and international experience to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether the use of taurine at levels up to 45 ppm (*i.e.*, 0.0045%) in enhanced water beverages (*i.e.*, flavored water beverages with other added ingredients such as vitamins and minerals), providing up to 29.3 mg taurine/day, is Generally Recognized as Safe (GRAS), based on scientific procedures. The Expert Panel consisted of the below-signed qualified scientific experts: Dr. Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine); Dr. I. Glenn Sipes, Ph.D., Fellow AAAS, ATS (University of Arizona); and Dr. Gary M. Williams, M.D., DABT, FRCP (New York Medical College). For purposes of the Expert Panel's evaluation, "safe" or "safety" indicates that there is a reasonable certainty of no harm under the intended conditions of use of the ingredient in foods, as stated in 21 CFR §170.3(i) (U.S. FDA, 2013).

The Expert Panel, independently and collectively examined a comprehensive package of scientific information and data pertinent to taurine compiled from the literature and other published sources through July 10, 2014. This information was presented in a dossier, "Documentation Supporting the Evaluation of Taurine as Generally Recognized as Safe (GRAS) for Use in Enhanced Water Beverages". In addition, the Expert Panel evaluated other information deemed appropriate, necessary, or pertinent, to the safety of the conditions of use of taurine. The data evaluated by the Expert Panel included information pertaining to the method of manufacture, product specifications and analytical data, the conditions of intended use of taurine in enhanced water beverages, dietary intake estimates for the intended use, and a comprehensive assessment of the available scientific literature pertaining to the safety of taurine.

Following independent and collaborative critical evaluation of such data and information, the Expert Panel met *via* teleconference on August 15, 2014. The Expert Panel unanimously concluded that taurine, meeting appropriate food-grade specifications and manufactured in accordance with current Good Manufacturing Practice (cGMP), is GRAS for use at a level of 45 ppm in enhanced water beverages, providing up to 29.3 mg taurine/day. In combination with supplemental uses of taurine and background dietary intakes (*i.e.*, up to 400 mg/day), the most conservative estimates of the mean and 90<sup>th</sup> percentile all-user intake of taurine are 424.8 and

442.6 mg/day for the total population. The GRAS determination was based on scientific procedures, and a summary of the basis for the Expert Panel's conclusion is provided below.

# SUMMARY AND BASIS FOR GRAS DETERMINATION

Taurine is manufactured by chemical synthesis in accordance with cGMP using safe and suitable food grade reagents and processing aids permitted for use in food in the United States (U.S.) and/or determined to be GRAS for use in the manufacture of taurine. The taurine added to enhanced water beverages is provided by outside suppliers and is of high purity and is compliant with specifications set forth by the Food Chemicals Codex (FCC, 2014), the U.S. Pharmacopeia (USP, 37<sup>th</sup> edition), and the Japanese Pharmacopoeia (JP, 15<sup>th</sup> edition) (JP, 2006; USP, 2014). The Expert Panel considered the adherence of the taurine ingredient to the FCC, USP, and JP specifications for taurine to support its suitability, under its conditions of manufacture, for use as a food ingredient. Taurine has a shelf-life of 3 years when stored in sealed polypropylene bags at ambient storage conditions. The Expert Panel reviewed batch analyses from several lots of taurine, as provided by three manufacturers, demonstrating that the ingredient is manufactured in a reproducible manner and is consistently compliant with physical, chemical, and microbiological specifications set forth by the FCC, USP, and JP (JP, 2006; FCC, 2014; USP, 2014).

There are currently no regulations governing the use of taurine in food in the U.S. However, taurine has been determined to be GRAS for use as a flavoring agent by the Flavor and Extract Manufacturers' Association of the United States (FEMA) [GRAS 17 (3813) – Smith *et al.*, 1996], and the addition of taurine as a nutrient to hypo-allergenic soy-based infant formula at levels consistent with cGMP is common practice by infant formula manufacturers in the U.S. and globally. Taurine occurs naturally in the diet as a component of meat, poultry, seafood, and dairy products, with estimated background dietary intakes varying widely depending on the types of food consumed (*i.e.*, ranging from 17 mg/day from lacto-ovovegetarian diets to 400 mg/day from omnivorous diets) (Rana and Sanders, 1986; Laidlaw *et al.*, 1990; Hayes and Trautwein, 1994). Dietary intake of taurine is negligible in those consuming a vegan diet. Taurine also is present in human milk and in infant formula at levels of 4 to 7 mg/100 mL, providing daily intakes of 8 to 14 mg/kg for a 5 kg infant consuming 1 L of infant formula or human milk/day (Laidlaw *et al.*, 1990; Hayes and Trautwein, 1994).

The proposed use of taurine in enhanced water beverages were estimated to result in a mean intake of 15.9 mg/day (0.24 mg/kg body weight/day) and a 90<sup>th</sup> percentile intake of 29.3 mg/day (0.45 mg/kg body weight/day). The individual population group with the highest estimated intakes resulting from the proposed food use was female adults, who displayed mean and 90<sup>th</sup> percentile intakes of 18.7 and 33.3 mg/day (0.26 and 0.45 mg/kg body weight/day, respectively).

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When dietary supplements containing taurine were added to the assessment, the mean intake in the total population increased to 24.8 (0.37 mg/kg body weight/day) while the 90<sup>th</sup> percentile level of intake increased to 42.6 mg/day (0.61 mg/kg body weight/day). Within the highest consumers of taurine, (*i.e.*, female adults), inclusion of supplement products in the assessment increased the mean and 90<sup>th</sup> percentile intakes to 29.3 mg/day (0.43 mg/kg body weight/day) and 64.0 mg/day (0.63 mg/kg body weight/day), respectively.

In addition to the consumption of taurine from the proposed food use and supplement products, the contribution of the background diet to the overall intake of taurine should be considered. As detailed in Section 5.1, the background diet is reported to provide up to 400 mg taurine/day. Therefore, the most conservative estimate of the mean and 90<sup>th</sup> percentile all-user intake of taurine from all sources (*i.e.*, enhanced water beverages, taurine-containing supplements, and background diet) would be 424.8 and 442.6 mg/day, respectively, for the total population. Among female adults, the addition of the background dietary intakes to the estimates for the consumption of taurine from the proposed food use and supplement products results in mean and 90<sup>th</sup> percentile intake estimates of 429.3 and 464.0 mg/day, respectively.

The National Health and Nutrition Examination Survey is a short term survey (*i.e.*, 2 days of data per cycle), and can therefore overestimate long-term consumption patterns of products that may be consumed relatively infrequently, such as enhanced water beverages. Estimates derived from these data are therefore considered to represent a worst-case illustration of potential intakes. Additionally, the assessments generated based on the proposed use level for taurine are based on the assumption that all enhanced water beverages consumed contain the maximum indicated quantity of taurine, which also may lead to an overestimation of the impact of the proposed use levels on the consumption of taurine among consumers of these products.

The Expert Panel reviewed published information characterizing the pharmacokinetics of taurine in rats and humans. Physiological taurine status is determined by dietary intake and from endogenous synthesis. In humans, taurine is considered a conditionally essential nutrient, as it is not synthesized at sufficient levels in newborn infants due to age-dependent expression of cysteine-sulfinic acid decarboxylase, the enzyme predominantly responsible for taurine synthesis in humans (Hayes and Trautwein, 1994). In humans and other mammals, endogenous production of taurine occurs in many tissues, including primarily the liver, brain, and pancreas (EFSA, 2012). As a nutrient, taurine is conjugated with bile acids in the liver, and also is required for cell membrane stabilization, osmoregulation, regulation of calcium flux, neuronal excitability, and may have anti-oxidant functions (Eudy *et al.*, 2013). Taurine is present at concentrations of 2 to 30 mM intracellularly and 35 to 100 µM in extracellular fluids in various mammalian tissues (*e.g.*, plasma, breast milk, and cerebrospinal fluid) (Chesney, 1985; Zelikovic and Chesney, 1989; Trautwein and Hayes, 1990). The total body pool of taurine has been estimated to range from 12 to 18 g (PDRNS, 2008).

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Following oral exposure in rodents and humans, taurine is rapidly absorbed via a β-amino acid or taurine active transport system in the small intestine (Sved et al., 2007; Ghandforoush-Sattari et al., 2010). In healthy, fasted human volunteers, maximum plasma levels of 0.47 to 0.90 mmol/L were attained within 1 to 2.5 hours following a taurine-rich meal or single oral dose of 4 g taurine (Trautwein and Hayes, 1995). Taurine has a plasma half-life of 0.7 to 1.4 hours, with plasma taurine concentrations in humans reported to return to baseline within 7 hours of consumption (Trautwein and Hayes, 1995; Ghandforoush-Sattari et al., 2010). Taurine is therefore not expected to bioaccumulate, even in individuals consuming unusually large amounts of taurine on a daily basis. This is illustrated by the marginal increases in plasma taurine concentrations reported within 12 to 24 hours of the last dose of taurine in subjects consuming 3 or 6 g taurine/day for 8 weeks or 7 days (respectively) (Zhang et al., 2004a; Rosa et al., 2014). Although these increases (approximately 71 and 97% in the 7-day and 8-week studies, respectively) were statistically significant, they are considered to be physiologically marginal compared to an increase of approximately 933% reported at T<sub>max</sub> (i.e., 1.5 hours; the time from dosing to maximal plasma concentration) 1 hour after consumption of 4 g taurine in humans (Ghandforoush-Sattari et al., 2010).

As taurine is a polar molecule, it is unable to cross cellular membranes. Tissue concentrations of taurine are under homeostatic control, with cellular uptake mediated by high-affinity, lowcapacity Na<sup>+</sup>/Cl<sup>-</sup> coupled transporters (Sturman et al., 1975). These transporters are saturated at normal plasma taurine concentrations, providing mechanistic support for the observation that tissue concentrations are not appreciably influenced by dietary intake (Sturman, 1973; Trautwein and Hayes, 1995; Sved et al., 2007). Results of studies conducted in Sprague-Dawley rats administered <sup>14</sup>C taurine orally at doses of 30 or 300 mg/kg body weight/day for up to 14 days indicate that exogenous taurine does not increase total brain taurine concentrations beyond baseline physiological levels (Sved et al., 2007). The European Food Safety Agency (EFSA) (EFSA, 2009) noted that this observation "largely rules out the possibility of stimulatory effects from taurine at the level of the central nervous system". Taurine is distributed to a wide range of tissues, with the highest concentrations observed in the muscle, heart, kidney, and liver; however, only a small quantity of exogenous taurine is exchanged with tissue pools. Radio-label studies in humans demonstrate that taurine is metabolically inert and is not subject to biotransformation events, with the exception of conjugation with bile acids (Sturman et al., 1975). Only a very small proportion of orally administered taurine (i.e., 5%) is incorporated into bile acids, with the majority recovered in the urine (Sturman et al., 1975). Small quantities of putative bacteria-derived sulfated conjugates also have been detected in the urine of humans orally and intravenously administered radiolabeled taurine (Sturman et al., 1975). Overall, the available data demonstrate that approximately 36 to 67% of orally administered taurine is rapidly absorbed from the gastrointestinal tract, following which it may be conjugated with bile acids and excreted through the biliary tract. Unconjugated taurine is widely distributed and rapidly equilibrated, with any excess taurine eliminated primarily via the kidneys.

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Consistent with results of pharmacokinetic studies (which demonstrate that supplemental taurine is metabolically inert, does not appreciably influence tissue concentrations, does not bioaccumulate, and is rapidly excreted in the urine unchanged), results of acute, subchronic, and long-term toxicity studies support the safety of taurine under the intended conditions of use (Takahashi *et al.*, 1972a; Kihara *et al.*, 1991; SCF, 2003). This conclusion is supported in part by the reported oral median lethal doses of >5,000 and >7,000 mg taurine/kg body weight in rats and mice, respectively (Drugs in Japan, 1990; Kihara *et al.*, 1991).

The long-term toxicity of taurine was evaluated in an 18-month study conducted by Takahashi *et al.* (1972a). No compound-related clinical, behavioral, hematological, or histological effects (*i.e.*, the latter regarding the cerebrum, cerebellum, myocardium, spleen, pancreas, gastrointestinal walls, or testes) were reported in Wistar rats (9 males and 7 females/group) given diets containing 0, 0.5, or 5% taurine (*i.e.*, providing reported doses of 0, 250, or 2,500 mg taurine/kg body weight/day, respectively). No significant effects on body weight were reported, and the observed decrease in ovary weight in treated females compared to controls may have been due to follicular enlargement (and associated increased ovary weight) observed in control females. Moderate dilation of bile capillaries was reported in high-dose males and females, although these effects were not associated with histological evidence of hepatic toxicity. A no-observed-adverse-effect level (NOAEL) was not established by the study authors, but a NOAEL of 5% taurine in the diet (*i.e.*, 2,500 mg/kg body weight/day), could be determined based on the results of this study.

The safety of taurine for use in enhanced water beverages is corroborated by the results of two 13-week studies considered pivotal by EFSA (2009) and the Scientific Committee on Foods (SCF) (1999, 2003) in their safety evaluations for taurine. In these 2 studies [conducted in accordance with current Good Laboratory Practice and Organisation for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals (Test No. 408) (OECD, 1998a,b)], rats (20/sex/group) were administered 0, 300, 600, or 1,000 mg taurine/kg body weight/day (by gavage; WIL, 2001); or 0, 600, or 1,000 mg taurine/kg body weight/day (by gavage) or approximately 1,100 or 1,650 mg taurine/kg body weight/day (*via* drinking water) (WIL, undated). The results of these studies have been critically reviewed by the European Commission (EC) SCF during the Agency's evaluation of the use of taurine in energy beverages.

Regarding the results of the first study (WIL, 2001), the SCF stated that taurine did not cause any persistent effects on body weight or food consumption, and the results of biochemical, hematological, urinalysis, and histopathological examinations were unremarkable. The results of functional observational battery (FOB) testing demonstrated detrimental effects on motor performance in high-dose animals, with marginal effects observed at the lower doses, and a clear effect on behavior at 1,000 mg/kg body weight/day. However, the SCF noted that similar effects on motor performance were not typically reported in other studies in which high doses of

taurine were administered intravenously or *via* the diet (*e.g.*, Takahashi *et al.*, 1972a; Friedman *et al.*, 1983). Following consultation with the laboratory (WIL, 2001), the SCF determined that FOB testing was not conducted using an appropriate and blinded scientific design; therefore a second 13-week study including focused neurological endpoints was conducted (EFSA, 2009).

In this second study (WIL, undated), no compound-related adverse effects on body weight, food consumption, clinical effects, or macroscopic observations were reported at any dose. In addition, no compound-related adverse effects on FOB parameters (*i.e.*, home cage, handling, open field, sensory, neuromuscular, and physiological observations) or locomotor activity were reported at any dose. The methodology and results of this study were considered sufficient for EFSA (2009) to derive a NOAEL for taurine of 1,000 mg/kg body weight/day for the original study reviewed by the SCF in 2003 (WIL, 2001). A NOAEL of 1,656 mg/kg body weight/day was determined following a 13-week exposure *via* drinking water, based on a lack of behavioral effects reported in the follow-up neurological study (WIL, undated). These studies (WIL, 2001; WIL, undated) were the subject of multiple critical evaluations conducted by qualified scientific experts, and the study summaries and expert opinions have been made publically available (SCF, 1999, 2003; EFSA, 2009). Accordingly, the study results were considered supportive of the current GRAS assessment for taurine intended for use in enhanced water beverages.

Several other repeated-dose studies were identified, in which safety parameters were reported upon consumption of taurine by mice, rats, and guinea pigs. Although these studies are not traditional toxicological studies, no significant, compound-related, physiologically relevant adverse effects were reported (Fujihira *et al.*, 1970; Cantafora *et al.*, 1986; Wang *et al.*, 1997; Akira *et al.*, 2013).

In the 5 reproductive and developmental toxicity studies evaluated by EFSA (2009) and the SCF (1999, 2003), no evidence of developmental toxicity attributable to taurine was reported upon oral administration of 300 to 4,000 mg taurine/kg body weight/day to pregnant mice or rats during gestation (Takahashi *et al.*, 1972b; Yamada *et al.*, 1981; Friedman *et al.*, 1983). Furthermore, no adverse developmental effects attributable to taurine were reported in a 3-generation study in which mice were continuously administered up to 7.0 g taurine/kg body weight/day (Takahashi *et al.*, 1972b), or in cats administered up to 416 mg taurine/kg body weight/day from 6 months prior to mating until weaning of offspring at 8 weeks of age (Sturman and Messing, 1992).

In an additional recently published study, rats were given control or obesogenic diets (CD or OD, respectively) providing 0 or approximately 1,500 mg taurine/kg body weight/day, from Gestational Day 1 until weaning of offspring at 3 weeks of age (Li *et al.*, 2013). In this study, increased expression of maternal hepatic genes related to lipogenesis and inflammation was reported in taurine-treated dams compared to their respective controls, although these changes were not associated with gross or histopathological effects indicative of hepatotoxicity. Li *et al.* (2013) reported increased neonatal mortality in pups born to CD dams supplemented with

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taurine compared to CD controls [i.e., 1.4 ± 0.1% in the CD group compared to 7.1 ± 4.0% in the CD-taurine group]. No explanation was given for this observation, but it may have related to the small decrease in maternal body weights of the CD-taurine group relative to CD controls. No comparison to historical data with respect to the range of infant mortality was provided. Thus, the toxicological significance of the reported increase in neonatal mortality is unknown. Adverse effects on offspring mortality were not reported in any of the other identified studies, even upon administration of taurine at higher doses and/or over longer periods of time. In addition, Li *et al.* (2013) reported no significant differences between groups with respect to litter size, pup sex ratio, pup body weight, or any measures of insulin resistance, inflammation, or lipid metabolism. Considering the overall weight of evidence and the SCF (1999, 2003) conclusion that taurine does not demonstrate any potential for teratogenicity, supplemental taurine intake is unlikely to exert adverse effects on reproductive or developmental parameters under the intended conditions of use.

The absence of mutagenic or genotoxic effects reported in reverse mutation, *Rec*, chromosomal aberration, or sister chromatid exchange assays (Laidlaw *et al.*, 1989; Yamada *et al.*, 1993; Cozzi *et al.*, 1995) indicates that taurine is not mutagenic or genotoxic. Taurine's lack of genotoxic potential is corroborated by its long history of use, a lack of structural alerts for genotoxicity, its endogenous nature, and natural occurrence in the human diet. In addition, the SCF (1999, 2003) concluded that based on the available toxicology studies, taurine does not exhibit any potential for genotoxicity or carcinogenicity.

The Expert Panel additionally evaluated a series of published studies in humans who consumed taurine at doses of 0.5 to 20 g/day for up to 20 weeks. These studies were conducted in healthy adults, and adults or children with a variety of chronic health conditions, and have been the subject of comprehensive and critical evaluations by Shao and Hathcock (2008) and EFSA (2009). Shao and Hathcock (2008) critically evaluated over 30 peer-reviewed published studies involving taurine consumption, and concluded that no significant adverse effects attributable to taurine consumption had been reported. Based on the results presented in these studies, Shao and Hathcock (2008) identified an Observed Safe Level (OSL¹) of 3,000 mg taurine/day. This conclusion was based in part on results of the study by Zhang *et al.* (2004a,b), who reported that consumption of 3,000 mg taurine/day by healthy adults for 7 or 12 weeks was not associated with adverse effects. EFSA (2009) concluded that available data on the consumption of taurine by humans "...do not give any indication of safety concern." and "Such information revealed that oral daily ingestion of taurine doses in the 3-6 g range for periods up to one year, did not produce adverse health effects", and identified an OSL of 6,000 mg/day (EFSA, 2012).

<sup>&</sup>lt;sup>1</sup> The OSL is an estimate of safe exposure in humans, represented as the highest intake with convincing evidence of safety that is applied without the use of additional safety factors.

An updated review of the published literature was conducted by Intertek (on July 10, 2014), and the results of the studies identified were consistent with previous results, supporting the conclusion that consumption of taurine has not been associated with adverse effects. Among the identified human studies, no adverse effects attributable to taurine were reported in subjects (with normal kidney function) consuming up to 20 g taurine/day for up to 6 weeks, or up to approximately 9 g taurine/day for 7 weeks to 1 year. In 1 study conducted in patients on chronic hemodialysis for renal failure, high doses of taurine (100 mg/kg body weight/day) were associated with vertigo and/or dizziness in 2 of 4 patients tested (Suliman *et al.*, 2002). These symptoms were attributed to the inability of the study subjects to excrete excess taurine, resulting in an accumulation of taurine in the plasma and muscle, as would be expected for any compound eliminated *via* the kidney. Accumulation of taurine is not expected to be of concern in those with normal kidney function.

One case study was identified in which an individual with known sulfite and sulfonamide allergies developed hypersensitivity to taurine (containing a SO<sub>3</sub> moiety) above a threshold level (estimated to be approximately 250 to 300 mg taurine) (Stohs and Miller, 2014). Challenge tests provided evidence for hypersensitivity to taurine. Although this individual had demonstrated allergies to a variety of substances, this is the first reported of taurine hypersensitivity.

The totality of information reviewed by the Expert Panel, as described herein, was sufficient to support a determination that the intended use of taurine in enhanced water beverages (at up to 45 ppm, providing up to 29.3 mg taurine/day) is safe and suitable and GRAS. Pivotal supporting data include the following:

- 1) Pharmacokinetic studies in humans and rats demonstrate that taurine is metabolically inactive, is rapidly excreted primarily unchanged in the urine, and does not bioaccumulate even when consumed in large quantities (i.e., 6 g/day). Dietary sources of taurine do not appreciably influence concentrations of taurine in various tissues, including the brain, for which transport of taurine is under homeostatic control.
- 2) A NOAEL of 2,500 mg/kg body weight, based on a lack of adverse effects reported in a long-term (18-month) dietary study in rats (Takahashi et al., 1972a); this NOAEL is supported by a lack of adverse effects reported in an 8-week dietary study in which male rats were given diets providing up to 5,000 mg taurine/kg body weight/day (Hwang et al., 2000), and the NOAELs of 1,000 and 1,650 mg/kg body weight/day (the highest doses tested) reported in the 2 unpublished 13-week studies considered pivotal to EFSA's and the SCF's safety assessments of taurine (WIL, 2001; WIL, undated 42306).
- 3) Negative findings in mutagenicity and genotoxicity studies, no evidence of carcinogenic potential, and a lack of reproductive or developmental toxicity.

- 4) Available human data [including studies evaluated by the SCF (1999, 2003), EFSA (2009), and Shao and Hathcock (2008), and those identified in a recent search of the published literature] demonstrate that the OSL for taurine intake in adults with normal kidney function is >20 g/day. This level of intake is approximately 375 times greater than the estimated intake of taurine from the intended conditions of use in enhanced water beverages, and ≥46.8 times greater than the estimated intakes of taurine from all sources including background dietary intakes (*i.e.*, up to 427.3 mg/day).
- 5) Taurine is a common constituent of the typical U.S. diet, is present in human milk and infant formula, and is synthesized endogenously, with total body pools of 12 to 18 g in adults.

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#### CONCLUSION

We, the undersigned independent qualified members of the Expert Panel, have individually and collectively critically evaluated the data and information summarized above, as well as other data and information that we deemed pertinent to the safety of the proposed use of taurine in enhanced water beverages. We unanimously conclude that the proposed use of taurine, produced in accordance with current good manufacturing practice and meeting appropriate food grade specifications, in enhanced water beverages at levels up to 0.0045%, providing up to 29.3 mg taurine/day, are safe and suitable and Generally Recognized as Safe (GRAS) based on scientific procedures.

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

	0 / May 2015 Date
Dr. Joseph F. Borzelleca, Ph.D. / Virginia Commonwealth University School of Medicine	Date
(b) (6)	
	06 HAC 2015
Dr. I. Glenn Sipes, Ph.D., Fellow AAAS, ATS University of Arizona	Date
(b) (6)	
	08 May 2015
Dr. Gary M. Williams, M.D., DABT, FRCP New York Medical College	Date <del>d</del>

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### Appendix B

**Certificates of Analysis** 

Compounds Taurine
Beverage Local Name (All)

Row Labels         Average of Result         Average of Total Amount           48         360         40           56         428         40           59         412         40	00 00 00
56     428     40       59     412     40	00 00 00
	00
	0
64 425 40	
72 426 40	00
76 425.5 40	
77 #DIV/0! 40	0
81 397 40	0
83 421 40	00
85 372 40	0
96 408 40	
98 371 40	
101 384 40	
105 #DIV/0! 38	
106 418 38	
111 402 40	
112 #DIV/0! 39	
118 405 40	
119 421.5 40	
127 394 38	
132 409.5 40	
135 #DIV/0! 38	
139 406 39	
140 411 40 147 427 40	
·=·	
-	
152 393 40 154 401.3333333 388.666666	
156 350 38 162 389.5 389	
169 412 389	
170 395 38	
171 #DIV/0! 38	
174 390 39	
176 410 38	
180 373 38	
187 407 39	
190 417 38	
192 413.5 389	
195 396 39	
197 386 39	
202 404 40	
211 #DIV/0! 38	
215 389 40	
216 419 38	1
218 404.5 38	7

<b>Grand Total</b>	402.7619048	392.9305556
(blank)	423	387
425	428	392
354	400	392
328	#DIV/0!	387
295	404	387
275	426.5	392
265	378	387
261	383	392
251	400	387
241	386	389.5
221	404	387

# S1402171C

#### **ORIGINAL**

### 上 黄冈市富驰制药有限责任公司 FUCHI PHARMACEUTICAL CO., LTD OF HUANGGANG CITY

#### CERTIFICATE OF ANALYSIS

PRODUCT: TAURINE JP15/USP36

BATCH NO.: **C002-YB1401155** REPORTED DATE: 2014/02/17 QUANTITY: 18000kg

MANU DATE: NOV 26 2013

EXP

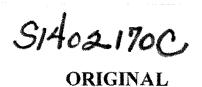
DATE: NOV 25, 2015

<b>Item</b>	USP36 Standard	JP15 Standard	Results
Characteristics	White Crystals Or White Crystalline Powder,Odorless	White Crystals Or White Crystalline Powder,Odorless	White Crystalline Powder,Odorless
Identification	Infrared Absorption	Infrared absorption Spectrum should conform to requirement	Conforms
рН	1	4.1~5.6	5.0
	Te	st	3
Clarity And Color Of Solution	Clear And Golorless	Clear And Colorless	Clear And Colorless
Heavy Metals	0.0015% Max	10ppm Max	10ppm Max
Chloride	0.05% Max	0.011% Max	0.011% Max
Sulphate	0.03% Max	0.010% Max	0.010% Max
Iron	0.003% Max	10ppm Max	10ppm Max
Ammonium	1,	0.02% Max	0.02% Max
Easily Carbonizable Substances	No Color Develops	1	Colorless
Related Subtances	/	Should conform to requirement	Conforms
Loss On Drying	0.3% Max	0.20% Max	0.15%
Residue On Ignition	0.3% Max	0.1% Max	0.1%
Chromatographic Purity	0.5% Max	/	0.2% Max
Total Plate Count	NMT 1000cfw/g	NMT 1000cfw/g	<10cfu/g
Yeasts And Molds	NMT 100cfu/g	NMT 100cfwg	20cfu/g
Salmonella	Negative	Negative	Conforms
E. Coli	Negative	Negative	Conforms
Staphylococcus Aureus	Negative/10g	Negative/10g	Conforms
Enterobacteriaceae	Negative/g	Negative/g	Conforms
			99.1%

Head Of Dept:Feng xiaohong

Reviewer:Li dan

Reporter: Xiong yan



## **E** 黄冈市富驰制药有限责任公司 FUCHI PHARMACEUTICAL CO., LTD OF HUANGGANG CITY

#### CERTIFICATE OF ANALYSIS

PRODUCT: TAURINE JP15/USP36

BATCH NO.: C002-YB1401156
REPORTED DATE: 2014/02/17

QUANTITY: 18000kg

MANU DATE: NOV 27, 2013

EXP DATE: NOV 26, 2015

REPORTED DATE:	2014/02/17 EXP DATE: NOV 26, 2015		JV 20, 2013
Item	USP36 Standard	JP15 Standard	Results
Characteristics	White Crystals Or White Crystalline Powder,Odorless	White Crystals Or White Crystalline Powder,Odorless	White Crystalline Powder,Odorless
Identification	Infrared Absorption	Infrared absorption Spectrum should conform to requirement	Conforms
рН	1	4.1~5.6	5.0
	Te	st	
Clarity And Color Of Solution	Clear And Colorless	Clear And Colorless	Clear And Colorless
Heavy Metals	0.0015% Max	10ppm Max	10ppm Max
Chloride	0.05% Max	0.011% Max	0.011% Max
Sulphate	0.03% Max	0.010% Max	0.010% Max
lron	0.003% Max	10ppm Max	10ppm Max
Ammonium	1.	0.02% Max	0.02% Max
Easily Carbonizable Substances	No Color Develops	1	Colorless
Related Subtances	1	Should conform to requirement	Conforms
Loss On Drying	0.3% Max	0.20% Max	0.14%
Residue On Ignition	0.3% Max	0.1% Max	0.1%
Chromatographic Purity	0.5% Max	/	0.2% Max
Total Plate Count	NMT 1000cfu/g	NMT 1000cfu/g	<10cfu/g
Yeasts And Molds	NMT 100cfu/g	NMT 100cft/g	<10cfu/g
Salmonella	Negative	Negative	Conforms
E. Coli	Negative	Negative	Conforms
Staphylococcus Aureus	Negative/10g	Negative/10g	Conforms
Enterobacteriaceae	Negative/g	Negative/g	Conforms
∧ssay/	98.5-101.5%	99.0-101.0%	99.1%
Conclusion	The Pr	oduct Conforming To JP15/USP:	16

Head Of Dept:Feng xiaohong

Reviewer:Li dan

Reporter: Xiong yan

#### **ORIGINAL**

## **声**黄冈市富驰制药有限责任公司 FUCHI PHARMACEUTICAL CO., LTD OF HUANGGANG CITY

#### **CERTIFICATE OF ANALYSIS**

PRODUCT: TAURINE JP15/USP36 -

BATCH NO.: C002-YB1401157 ~

QUANTITY: 18000kg

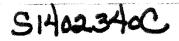
MANU DATE: DEC 22, 2013

REPORTED DATE	: 2014/03/11		DEC 21, 2015
Item	USP36 Standard	JP15 Standard	Results
Characteristics	White Crystals Or White Crystalline Powder, Odorless	White Crystals Or White Crystalline Powder,Odorless	White Crystalline Powder,Odorless
Identification	Infrared Absorption	Infrared absorption Spectrum should conform to requirement	Conforms
рН	· · · · · · · · /	4.1~5.6	5.0
	Te	st	
Clarity And Color Of Solution	Clear And Colorless	Clear And Colorless	Clear And Colorless
Heavy Metals	0.0015% Max	10ppm Max	10ppm Max
Chloride	0.05% Max	0.011% Max	0.011% Max
Sulphate	0.03% Max	0.010% Max	0.010% Max
Iron	0.003% Max	10ppm Max	10ppm Max
Ammonium	1	0.02% Max	0.02% Max
Easily Carbonizable Substances	No Color Develops		Colorless
Related Subtances	/	Should conform to requirement	Conforms
Loss On Drying	0.3% Max	0.20% Max	0.14%
Residue On Ignition	0.3% Max	0.1% Max	0.1%
Chromatographic Purity	0.5% Max	/	0.2% Max
Total Plate Count	NMT 1000cfu/g	NMT 1000cfw/g	<10cfu/g
Yeasts And Molds	NMT 100cfu/g	NMT 100cfu/g	<10cfu/g
Salmonella	Negative/25g	Negative/25g	Conforms
E. Coli	Negative/10g	Negative/10g	Conforms
Staphylococcus Aureus	Negative/10g	Negative/10g	Conforms
Enterobacteriaceae	Negative/g	Negative/g	Conforms
Assay (5	98.5-101/5%	99.0-101.0%	99.0%
Conclusion	The Pro	duct Conforming To JP15/USP36	<b>,</b>

Head Of Dept: Fengaria ohong

Reviewer:Li dan

Reporter: Xiong yan



### 江陰華昌食品添加劑有限公司 Jiangyin Huachang Food Additive Co., Ltd.

#### 检验报告 Certificate of analysis

订单编号 (Order Numbers):	FH1401007-1	地址,江苏省江阴市璜土镇瓦沿桥堍
报告日期 (Date):	11 March 2014	Add.: Wa Yan Qlao Tu, Huang Tu Town, Jiang Yin City, Jiang Su Province, China
报告页数 (Page):	I.	电话(Tel): +86-510-86056798,86056863,86058677
		传真(Fax): +66-510-86053331

样晶名称 Name of Sample	牛磺酸 Tauring	生产日期 Production Date	07 March 2014
批号 Batch NO.	1403062	检验日期 Analysis date	08 March 2014
批 量 Quantity	3000KG	报告日期 Report date	11 March 2014
质量标准 quality standard	JP15 and USP36	有效期 Exp date	06 March 2017

2 独项日 analytical items	规定 requirement	结果 results
t状 Discription	无色或白色结晶,或白色结晶性粉末 colorless or white crystals, or a white crystalline powder.	白色结晶性粉末 white crystalline powder
SM Identification	显正结果 (Positive)	呈正结果(Positive)
EM Identification	pli Value : between 4.1 and 5.6	5, 03
电度 Purity		
1)溶液的颜色与澄消度 Harity and color of solution	准清、无色 (clear and colorless)	符合规定 meet the requirement.
2〉色谱纯度 Chromatographic purity	个別杂质 (IndividualImpurities)<0.5%	<0.5%
(3)氧化物 Chloride	不超过(no more than) 0.011%	<0.005%
(4)硫酸盐 Sulfate	不超过(no more than) 0.010%	<0.010%
(5) 铵雄 Ammonium	不起过(no more than) 0,02%	<0.02%
(6)重金属 Heavy metals	不超过(no more than) 10ppm	<sppm< td=""></sppm<>
(7)铁盐 Iron	不超过(no more than) 10ppm	<2. Sppm
(8)有关物质 Related substances	不超过(no more than) 0.2%	<0.2%
干燥失重 Loss on drying	不超过(no more than) 0.2%	0, 16%
炽灼残渣 Rewidue on ignition	不超过(no more than) 0,1%	Ü, 10%
细菌总数 Total plate count	不超过(no sore than) 1000cfu/g	<10cfu/g
赛萬/酵母蘭 Wold/Yeast	不超过(no more than) 100cfu/g	· <10cfu/g
大肠杆菌 E. Coll	不得检出 Negative	未检出 No Found
大肠資群 Coliform	不得检图 Negative	未检出 No Found
全黄色葡萄球菌 Staphylococcus aureus	不得檢出 Negative	未捡出 No Found
點杆菌科 Enterobacteriacene	不得检出 Negative	未拉出 No Found
沙门氏菌 Salmonella	不得检出 Negative	· 未检出 No Found
含量 Assay	接干燥品计应为99.0%-101.0% when dried, contains not less than 99.0% and not were than 101.0% of C <sub>2</sub> H <sub>2</sub> NO <sub>2</sub> S	99, 19%

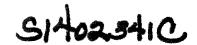
结论 CONCLUSION, 符合JP15和USP36要求 complies with JP15 and USP38

(b) (6) 检验员

(b) (6)

质量技术主管

QC主旨



#### 多江陰華昌食品添加劑有限公司 Jiangyin Huachang Food Additive Co..Ltd.

#### <u>检验报告</u> Certificate of analysis

订单编号 (Order Numbers):	FH1401007-1	<b>地址,江苏省江阳市瑞士镇瓦沿桥境</b>
报告日期 (Date):		Add: Wa Yan Qiao Tu, Huang Tu Town, Jiang Yin City, Jiang Su Province, China
报告页数 (Page):		电话(Tel)。+86-510-86056798,86056883,86058677
		传真(Fax): +86-510-86053331

拌品名称 Name of Sample	牛磺酸 Tauring	生产日期 Production Date	07 March 2014
批 号 Batch NO.	1403063	检验日期 Analysis date	08 March 2014
批 量 Quantity	3000KG	报告日期 Report date	11 March 2014
质量标准 quality standard	JP15 and USP36	有效期 Exp date	06 March 2017

i教項目 analytical items	規定 requirement	结果 results
杖 Discription	光色或白色结晶,或白色结晶性粉末 colorless or white crystals, or a white crystalline powder.	白色结晶性粉末 white crystalline powder
M Identification	呈正结果(Positive)	星正结果 (Positive)
279 Identification	pH Value: between 4.1 and 5.6	5. 03
t度 Purity		
1)溶液的颜色与澄清度 larity and color of solution	澄清、无色 (clear and colorless)	符合規定 meet the requirement
2)色谱统度 Chromatographic purity	个别杂质 (Individualimpurities)<0.5%	<0. ₹%
3) 氧化物 Chloride	不超过(no more than) 0.011%	<0, 005%
A)硫酸盐 Sulfate	不超过(no more than) 0.010%	<0.010%
(5) 铵盐 Ammonium	不過过(no more than) 0.02%	<0.02%
(6)重金属 Heavy metals	不超过(no more than) 10ppm	<5рра
(7)铁盐 Iron	不超过(no more than) 10ppm	<2. 5ррв
(8)有关物质 Related substances	不超过(no more than) 0.2%	<0.2%
干燥失重 Loss on drying	不翻过(no sore than) 0.2%	^`0.08%
以均残渣 Residue on ignition	不超过(no more than) 0.1%	0.10%-
细菌总数 Total plate count	不超过(no more than) 1000cfu/g	<10cfu/g
霉漢/酵母菌 Mold/Yeast	不超过(no more than) 100cfu/g	<10cfu/g
大肠杆菌 E. Coll	不得检出 Negative	未检出 No Found
大肠菌群 Collform	不得检出 Negative	未检出 No Found
全黄色葡萄球菌 Staphylococcus aureus	不得检出 Negative	未检出 No Found
版件面料 Enterobacturiaceae	不得检出 Negative	未捡出 No Found
沙门氏衛 Salsonella	不得輸出 Negative	未检出 No Pound
含量 Ansay	按干燥品计应为99.0%~101.0% when dried, contains not less than 99.0% and not sore than 101.0% of C <sub>2</sub> H <sub>2</sub> NO <sub>2</sub> S	99.08%

结论 CONCLUSION, 符合JP15和USP36要求 complies with JP15 and USP36

(b) (6) 检输员

(b) (6)

质量技术主管

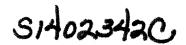
Kirtua (UKK) Arta III ka

Inspector

chief of QC

。QC主管

chief of quality and technolog 四回被专用意



### 江陰華昌食品添加劑有限公司 Jiangyin Huachang Food Additive Co., Ltd.

#### 检验报告 Certificate of analysis

订单编号(Order Numbers):	FH1401007-1	地址,江苏省江阴市项土镇瓦沿桥堍
报告日期(Date):	11 March 2014	Add.: Wa Yan Qiao Tu,Huang Tu Town,Jiang Yin City, Jiang Su Province, China
报告页数(Page):	1	电话(Tel):+86-510-86056798,86056883,86058677
		传真(Fax): +86-510-86053331

样品名和	* Name of Sample	牛磺酸 Taurine	生产日期 Production Date	07 March 2014
批号	Batch NO.	1403064	检验日期 Analysis date	08 March 2014
批量	Quantity	30 <b>00KG</b>	报告日期 Report date	11 March 2014
质量标为	quality standard	JP15 and USP36	有效期 Exp date	06 March 2017

全验项目 analytical items	规定 requirement	结果 results
生状 Discription	无色或白色结晶。或白色结晶性粉末 colorless or white crystals, or a white crystalline powder.	白色结晶性粉末 white crystalline powder
*N Identification	呈正结果(Positive)	呈正结果 (Positive)
# 33 Identification	pH Value: between 4.1 and 5.6	4. 97
图度 Purity		
1)溶液的颜色与理清度 larity and color of solution	澄清、无色 (clear and coloriess)	符合規定 meet the requirement
(2)色谱纯度 Chromatographic purity	个别杂版 (IndividualImpurities)<0.5%	<0.5%
(3) 氯化物 Chloride	不超过(no more than) 0.011%	<0.005%
(4) 寬殷盐 Sulfate	不超过(no more than) 0.010%	<0.010%
(5) 後輩 Armonium	不超过(no more than) 0.02%	<0.02%
(6) 重金属 Henry metals	不超过(no more than) 10ppm	<5р <sub>РМ</sub>
(7)铁盐 Iron	不超过(no more than) 10ppm	<2. 5рря
(8)有关物质 Related substances	不超过(no more than) 0.2%	<0, 2%
		. / / /
干燥失重 Loss on drying	不超过(no more than) 0.2%	0, 07%
以均残渣 Residue on ignition	不超过(no more than) 0.1%	0.10%
细菌总数 Total plate count	不超过(nu more than) 1000cfu/g	<10cfu/g
海蘭/酵母蘭 Mold/Yeast	不超过(no more than) 100cfu/g	* <10cfu/g
大肠杆菌 E. Coli	不得檢出 Negative	未检出 No Found
大肠菌群 Coliform	不得检出 Negative	未包出 No Found
全英色葡萄球菌 Staphylococcus aureus	不得检出 Negative	未检出 No Found
肠杆菌科 Enterohacteriaceae	不得检出 Negative	未检出 No Found
沙门氏衛 Salmonella	不得检出 Negative	未检出 No Found
含量 Assay	按干燥品计应为99.0%-101.0% when dried, contains not loss than 99.0% and not more than 101.0% of C.H.NO.S	99,08%

结论 CONCLUSION, 符合JP15和USP36要求 complies with JP15 and USP36

(b) (6) 檢驗员

C主管。

(b) (6)

**頭 攤 技 术 主 管** 

(b)

Inspector chief of QC chief of quality and technology
Notice:1.未加盡品管部印章无效。(It is invalid without original seal of quality management department)
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#### QIANJIANG YONGAN PHARMACEUTICAL CO., LTD.

No. 16 Zhuze Raod, Zekou, Qianjiang, Hubei, China Tel: 0086-728-6201-636 Fax: 0086-728-6202-797

#### TAURINE STABILITY RESEARCH TESTING DATA

This product stability test report is according to CP 2000 appendix XIXC: and the procedure is conform to Medical stability test principle;

- (1) sample source: usual product 3 batch, standard product 1 batch
- (2) Batch number: 20020304 20020305 20020306 0202006 (standard product)
- (3) storage packaging: two-poly plastic sealed packing.
- Deffect factor testing
- (a) put the sample into opened weighing bottle, put them into 60°C ± 2°C Constant-temperature Oven;
- (b) put the sample into opened weighing bottle, put them into RH92.5% vessel;
- (c) put the sample into opened weighing bottle, put them into illumination oven which installed daylight lamp, under 4500Lx ± 500Lx illumination condition.
- ②Accelerate testing Temperature: 40°C±2°C, RH75%±5%, airproof
- 3long-term testing Temperature: 25°C ± 2°C, RH60% ± 10%, airproof
- (4) testing period
- effect factor testing: 0 day, 5 days, 10 days
- Acclerate testing: 1 month, 2 months, 3 months, 6 months
- Long-time testing: 0 month, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 36 months, 48 months, 60 months
- (5) testing equipment: Electrothermal constent-temperature cultivation oven (type: 101-2A)
  - Spectrophotometer (type: WFZ800-D3B)
  - Analytical Balance (Type: TG328A)
  - Acidity meter (Type: PHS-3C)
  - Silica gel G254 lamina and relevant layer analytical vat
- (6) testing according as: CP 2000 section 2
- (7) testing item: appearance, assay, loss on drying, transmittance, relevant substance
- (8) testing result: see attached form one to six.
- (9) examination conclusion
- ①After high-heat destroy the sample, compare 10 days to 0 day, couldn't find any obvious changing, quality is relatively stable.
- ②After strong ray destroy the sample , compare 10 days to 0 day, couldn't find any obvious changing, quality is relatively stable.
- ③After heave humidity destroy the sample, compare 10 days and 0 day, except for some increasing of loss on drying, couldn't find other obvious changing, quality is relatively stable.
- (4) Within 6 months Accelerate testing the sample is relatively stable.



- ®With in 48 months long-time testing the sample is relatively stable.
- Still continue the long-time testing.

#### APPENDIX:

TABLE 1: batch 20020304 effect factor testing result:

Condition	Time of preservation	appearance	Assay ( anhydrous)	Loss on drying	transmittance	relevant substance
Imitial	0 day	White crystal	99.3%	0.12%	98.9%	Qualified
60°C±2°C	5 days	White crystal	99.1%	0.10%	99.1%	Qualified
pyrogenation	10 days	White crystal	99.2%	0.08%	98.9%	Qualified
4500Lx±	5 <b>days</b>	White crystal	99.3%	0.12%	99.3%	Qualified
500Lx	10 days	White crystal	99.4%	0.13%	99.1%	Qualified
RH92.5%	5 days	White crystal	99.0%	2.1%	98.9%	Qualified
humidity	10 days	White crystal	99.1%	4.3%	98.8%	Qualified

TABLE 2: batch 0202006 (standard product) effect factor testing result:

Condition	Time of preservation	appearance	Assay ( anhydrous)	Loss on drying	transmittance	relevant substance
Initial	0 day	White crystal	99.5%	0.14%	99.2%	Qualified
60℃±2℃	S days	White crystal	99.2%	0.11%	99.0%	Qualified
pyrogenation	10 days	White crystal	99.3%	0.08%	99.0%	Qualified
4500Lx±	5 days	White crystal	99.2%	0.13%	99.2%	Qualified
500Lx illumination	10 days	White crystal	99.2%	0.13%	99.1%	Qualified
RH92.5%	5 days	White crystal	99.4%	2.0%	98.9%	Qualified

	1.3						ł
Instrumental design	10 days	White crystal	99.3%	4.2%	98.9%	Qualified	į
humidity	10 days	Winte Crystal	22.370	4.270	70.776	Common	į
		7 1			F.,		1

TABLE 3: Batch 20020304 acceleration test and long time preservation:

Condition	Time of preservation	appearance	Assay (anhydrous)	Loss on drying	transmi ttance	relevant substance
Initial	0 month	White crystal	99.3%	0.12%	98.9%	Qualified
Accelerate	1 month	White crystal	99.2%	0.13%	99.0%	Qualified
testing	2 months	White crystal	99.3%	0.14%	99.0%	Qualified
10℃±2℃,	3 months	White crystal	99,1%	0.16%	99.2%	Qualified
RH75% ± 5%	6 months	White crystal	99.3%	0.18%	99.1%	Qualified
	3 months	White crystal	99.2%	0.13%	99.2%	Qualified
	6 months	White crystal	99.2%	0.14%	99.1%	Qualified
Long time	9 months	White crystal	99.4%	0.15%	99.2%	Qualified
testing	12 months	White crystal	99.0%	0.14%	98.8%	Qualified
RH60% ± 10%	18 months	White crystal	99.2%	0.16%	99.1%	Qualified
	24 months	White crystal	99.3%	0.14%	99.2%	Qualified
	36 months	White crystal	99.1%	0.14%	99.0%	Qualified



Table 4: Batch 20020305 acceleration test and long time preservation:

Condition	Time of preservation	appearance	Assay ( anhydrous)	Loss on drying	transmi ttance	relevant substance
Initial	Omonth	White crystal	99.1%	0.10%	99.2%	Qualified
Accelerate	1months	White crystal	99.0%	0.12%	99.2%	Qualified
testing	2months	White crystal	99.1%	0.14%	99.0%	Qualified
40°C±2°C,	3months	White crystal	99.1%	0.15%	99.1%	Qualified
RH75% ± 5%	<b>6months</b>	White crystal	99.2%	0.17%	99.3%	Qualified
long time	3months	White crystal	99.2%	0.11%	98.9%	Qualified
testing	<b>6months</b>	White crystal	99.1%	0.12%	99.1%	Qualified
25°C±2°C,	9months	White crystal	99.3%	0.14%	99.0%	Qualified
RH60% ± 10%	12months	White crystal	99.2%	0.15%	98.9%	Qualified
	18months	White crystal	99.0%	0.16%	99.0%	Qualified
	24months	White crystal	99.1%	0.14%	99.0%	Qualified
	36months	White crystal	99.0%	0.15%	99.2%	Qualified



Table5: batch 20020306 acceleration test and long time preservation

Condition	Time of preservation	appearance	Assay ( anhydrous)	Loss on drying	transmittance	relevant substance
Initial	Omonth	White crystal	99.4%	0.10%	99.3%	Qualified
accelerate	1months	White crystal	99.2%	0.11%	99.0%	Qualified
testing	2months	White crystal	99.3%	0.13%	99.2%	Qualified
40°C±2°C,	3months	White crystal	99.3%	0.14%	99.2%	Qualified
RH75%±	6months	White crystal	99.1%	0.14%	99.0%	Qualified
long time	3months	White crystal	99.4%	0.11%	99.0%	Qualified
testing	6months	White crystal	99.2%	0.10%	99.2%	Qualified
25℃±2℃,	9months	White crystal	99.2%	0.12%	99.2%	Qualified
RH60%±	12months	White crystal	99.1%	0.13%	99.1%	Qualified
	18months	White crystal	99.3%	0.15%	99.0%	Qualified
	24months	White crystal	99.3%	0.16%	99.2%	Qualified
	36months	White crystal	99.0%	0.16%	99.1%	Qualified

Table6: batch 0202006 acceleration test and long time preservation

Condition	Time of preservation	appearance	Assay ( anhydrous)	Loss on drying	transmittance	relevant substance
Initial	Omonth	White crystal	99.5%	0.14%	99.2%	Qualified
Accelerate	1 months	White crystal	99.4%	0.14%	99.0%	Qualified
testing	2months	White crystal	99.3%	0.16%	99.0%	Qualified
40℃±2℃,	3months	White crystal	99.4%	0.17%	99.0%	Qualified
RH75% ± 5%	6months	White crystal	99.2%	0.20%	99.1%	Qualified
	3months	White crystal	99.2%	0.15%	99.4%	Qualified
long time	<b>6months</b>	White crystal	99.4%	0.14%	99.1%	Qualified
testing	9months	White crystal	99.4%	0.16%	99.2%	Qualified
25°C±2°C, RH60%±10%	12months	White crystal	99.1%	0.17%	99.3%	Qualified
	18months	White crystal	99.2%	0.16%	99.1%	Qualified
	24months	White crystal	99.0%	0.18%	98.9%	Qualified
	36months	White crystal	99.1%	0.18%	98.9%	Qualified

DATE: AUG 16th, 2005

Stamp:



S1401746C

#### CERTIFICATE OF ANALYSIS

MANUFACTURER: QIANJIANG YONGAN PHARMACEUTICAL CO., LTD ADDRESS: NO.16 ZHUZE ROAD, QIANJIANG, HUBBI CHINA PHONE NO.86 728 6201636

Name of product: TAURINE USP33	CAS No.107-35-7	P/O.: P13008191
Batch size:3600kgs	Packing in 25kg/carton	Batch No., XB13123005
Manufacture date: 2013-12-03	Expiry date: 2016-12-02	Reported date: 2013-12-08

	Standard of JP8	Standard of USP36	Testing Data
haracteristics:	A white crystalline powder, od	lorless	A white crystalline powder, odorless
.Identification:	Positive	Positive	Positive
2.Clarity and color of solution:	Clear and colorless	9-4-4-0-7-4-4-4-4-4-4-4-4-4-4-4-4-4-4-4-4	Pass test
3.Chloride:	0.011%max	0.05%max	<0.010%
4.Sulfate:	0.014%max	0.03%max	<0.010%
5.Ammonium:	0.02%max		<0.015%
5.lron:		0.003% max	<0.001%
7.Heavy metals:	20ррпа глах	15ppm max	<8ppm
8.Arsenic:	2ppm max	******	<1ppm
9. Easily carbonizable substances:	No color develops		Colourless
10 Loss on drying:	0.2%(105℃, 2 hours)max	0.3%(105°C, 3hours)max	0.10%
11. Residue on ignition:	0.1%max	0.3%max	0.06%
12. Related compounds:	- un aparentina mentiti na migra	0.5% max	<0.5%
13. Assay (anhydrous):	98.5%min	98.5%~101.5%	99.2%
14.Total plate count;	NMT 1000/g	NMT 1000/g	55/g
15. Mold:	NMT 100/g	NMT 100/g	<10/g
16. Yeast:	NMT 100/g	NMT 100/g	<10/g
17. E. coli:	Negative/10g	Negative/10g	Not found
18.Salmonella:	Negative/25g	Negative/25g	Not found
19 Staphylococcus aureus:	COMPANY AND REPORT OF THE PROPERTY OF THE PROP	Negative/10g	Not found
20.Coliforms:	Negative/10g	Negative/10g	Not found
21.Enterobacteriaceae(enrichment method)	mandre dus laurens envisant des Angléteurs des	and the same payment of the same	Negative/25g

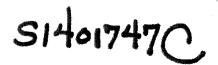
Conclusion: Comply with JP8/USP36

We hereby declare our product comply with GMP, ISO9001:2008. ISO22000. We hereby certify our product is BSE/TSE free.

Authorizer:

Checker:

Tester:



#### CERTIFICATE OF ANALYSIS

MANUFACTURER: QIANJIANG YONGAN PHARMACEUTICAL CO., LTD ADDRESS: NO.16 ZHUZE ROAD, QIANJIANG, HUBEI, CHINA PHONE NO.86 728 6201636

Name of product: TAURINE USP33	CAS No.107-35-7	P/O.: P13008191
Batch size:3600kgs	Packing in 25kg/carton	Batch No.: XB13123006
Manufacture date: 2013-12-07	Expiry date: 2016-12-06	Reported date: 2013-12-12

	Standard of JP8	Standard of USP36	Testing Data
haracteristics:	A white crystalline powder, odorless		A white crystalline powder, odorless
Identification:	Positive	Positive	Positive
2.Clarity and color of solution:	Clear and colorless		Pass test
3.Chloride:	0.011%max	0.05%max	<0.010%
1.Sulfate:	0.014%max	0.03%max	<0.010%
5.Ammonium:	0.02%rnax		<0.015%
S.lron:		0.003% max	<0.001%
7.Heavy metals:	20ppm max	15ppm max	<8ppm
8, Arsenic:	2ррт глех	electrical delication of the contract of the c	<1ppm
9. Easily carbonizable substances:	No color develops		Colouriess
10.Loss on drying:	0,2%(105°C, 2 hours)max	0.3%(105°C, 3hours)max	0.16%
11. Residue on ignition;	0,1%max	0.3%max	0.07%
12. Related compounds:		0.5% max	<0.5%
13.Assay (anhydrous):	98.5%min	98.5%~101.5%	99.2%
14. Total plate count:	NMT 1000/g	NMT 1000/g	.55/g
}5. Mold:	NMT 100/g	NMT 100/g	<10 g
16. Yeast:	NMT 100/g	NMT 100/g	<10 g
17. E. coli:	Negative/10g	Negative/10g	Not found
18.Salmoneiia.	Negative/25g	Negative/25g	Not found
19.Staphylococcus aureus:	and the disconnections for the survey reprinted the of the plant discount of the	Negative/10g	Not found
20.Coliforms	Negative/10g	Negative/10g	Not found
21.Enterobacteriaceac(enrichment	apon the money or whomas a surrein management of which where in	180 Film Charles on the Art of the Spiritual Street of Transport of Transport	Negative/25g

Conclusion: Comply with JP8/USP36

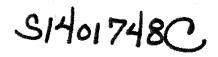
We hereby declare our product comply with GMP, ISO9001:2008. ISO22000. We hereby certify our product is BSE/TSE free.

Authorizer:



Tester:





### CÉRTIFICATE OF ANALYSIS

# MANUFACTURER; QIANJIANG YONGAN PHARMACEUTICAL CO., LTD ADDRESS: NO.16 ZHUZE ROAD, QIANJIANG, HUBEI, CHINA PHONE NO.86 728 6201636

Name of product: TAURINE USP33	CAS No.107-35-7	P/O.: P13008191
Batch size:600kgs	Packing in 25kg/carton	Batch No.: XB13123007
Manufacture date: 2013-12-07	Expiry date: 2016-12-06	Reported date: 2013-12-12

	Standard of JP8	Standard of USP36	Testing Data
Characteristics:	A white crystalline powder, odorless		A white crystalline powder, odorless
I.Identification:	Positive	Positive	Positive
2.Clarity and color of solution:	Clear and colorless		Pass test
3.Chloride:	0.011%max	0.05%max	<0.010%
1.Sulfate:	0.014%max	0.03%max	<0.010%
5.Ammonium:	0.02%max	47.26 (Mart - Co. C.	<0.015%
6.1ron:		0.003% max	<0.001%
7.Heavy metals:	20ppm max	15ppm max	<8ppm
8.Arsenie:	2ppm max		<1ppm
9.Easily carbonizable substances:	No color develops	***************************************	Colourless
10.Loss on drying:	0.2%(105°C, 2 hours)max	0.3%(105°C, 3hours)max	0.10%
11. Residue on ignition:	0.1%max	0.3%max	0.08%4
12. Related compounds:		0.5% max	<0.5%
13. Assay (anliydrous):	98.5%min	98.5%~101.5%	99.2%
14 Total plate count:	NMT 1000/g	NMT 1000/g	55/@
(5, Mold:	NMT 100/g	NMT 100/g	<10/6
In Yeast	NMT 100/g	NMT 100/g	<10/2
17. E. coli:	Negative/10g	Negative/10g	Not found
18.Salmonella:	Negative/25g	Negative/25g	Not found
19.Staphylococcus aureus:	and the state of t	Negative/10g	Not found
20.Colifornis	Negative/10g	Negative/10g	Not found
21.Enterobacteriaceae(enrichment method)	and the state of the State is not a wind of the state is not a state of the state is not a state of the state		Negative/25g

Conclusion: Comply with JP8/USP36

We hereby declare our product compress at GNP, ISO9001:2008. ISO22000. We hereby certify our product is BSE/TSE free.

Authorizer:

Checker: 5

Cester:

Pages 000067-000797 have been removed in accordance with copyright laws. The list of the removed references can be found on pages 000028-000032.