Petition for addition to the National List of the substance TAURINE, for use in infant formula products labeled as "organic."

INTRODUCTION

In October 1995, the National Organic Standards Board (NOSB) received a recommendation from its Processing, Handling and Labeling Committee ("the Committee") regarding the inclusion of synthetic vitamins, minerals, and accessory nutrients in organic foods.

The Committee had debated the issue of the inclusion of synthetic vitamins, minerals, and/or accessory nutrients in organic foods. Although it is generally considered that foods themselves are the best source of nutrients, in some cases, State regulations mandate the inclusion of vitamins and/or minerals to fortify foods.

The Committee also believed that recommendation by independent professional associations may also be taken into consideration. An example of this is infant cereals in which fortification of iron is highly recommended by the American Dietetic Association and various associations dealing with pediatric care and nutrition as a baby's stored iron supply from before birth runs out after the birth weight doubles.

The NOSB approved a Final Board Recommendation ("FBR") in October 1995. The Final Board Recommendation reads as follows:

> **"**Upon implementation of the National Organic Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic must be limited to that which is required by regulation or recommended for enrichment and fortification by independent professional associations."

The FBR includes a definition of the term "accessory nutrients," to mean nutrients not specifically classified as a vitamin or mineral but found to promote optimal health. Examples specifically cited in the FBR are omega-3 fatty acids, inositol, choline, carnitine, and taurine.

Infant formulas serve as the sole item of diet of infants who are not fed human milk for the first four to six months of life. Several accessory nutrients are included in infant formula for one or more of the following reasons:

1. their inclusion has been shown to enable infants fed these formulas to grow and develop similar to infants fed human milk;
2. their inclusion provides the infant with the same quantity of an accessory nutrient provided by human milk; and
3. the accessory nutrient is essential for one or more other species of mammal, which is indirect evidence of its biological essentiality for man.

In creating the current regulation for organic foods, Code of Federal Regulations, Title 7, Part 205, the USDA implemented the FBR with respect to permitting the addition of nutrient vitamins and minerals at §205.605(b), albeit with an annotation ("in accordance with 21CFR 104.20")

different than that approved by the NOSB. However, the current regulation is silent with respect to accessory nutrients.

On November 3, 2006, the USDA National Organic Program notified Accredited Certifiers that they could allow additional nutrients to be utilized in products certified as "organic" in accordance with 21 CFR 104.20(f).

In 2011 the Food and Drug Administration (FDA), at the request of NOP, provided its interpretation that 21 CRF 401.20 includes only those nutrient vitamins and minerals listed in 21 CFR 104.20(d)(3) and those identified as essential nutrients in 21 CFR 101.9.

On April 26, 2011, the Deputy Administrator of the National Organic Program announced its intention to publish draft guidance that will clarify the allowance of nutrient vitamins and minerals under the NOP regulation §205.605(b), according to the Food and Drug Administration's interpretation of 21 CFR 104.20.

Each of the "accessory nutrients" cited in the FBR are currently added to infant formula. Two of these "accessory nutrients" – choline and inositol - are actually vitamins according to the infant formula regulations for infant formula established by the Food and Drug Administration in the Code of Federal Regulations, Title 21, at §107.10 and §107.100.

Two other nutrients cited in the FBR and currently added to infant formula are carnitine and taurine. Both are less well-known amino acids that are essential to animal metabolism.

This petition specifically requests addition of taurine to the National List for use in infant formulas labeled as "organic."

Note that taurine is established as an essential nutrient required in the diet of cats. A petition requesting allowance of taurine in "organic" pet foods intended for cats recently was submitted for evaluation by the National Organic Standards Board. Much of the information in that petition is applicable to this petition, so it will be included by reference herein.

ITEM A

This petition seeks inclusion of TAURINE on the National List at §205.605 as a Non-agricultural (non-organic) substances allowed as an ingredient in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))."

ITEM B

1. The substance's chemical or common names.

The chemical name of taurine is 2-aminoethanesulfonic acid. Other names for taurine are 2-aminoethylsulfonic acid and 2-sulfoethylamine.

Taurine is a small, sulfur-containing β-amino acid with a sulfonic acid group rather than the carboxyl group typical of α-amino acids isolated from proteins. Taurine is an intracellular amino acid found in most tissues. Since it is a β-amino acid, taurine is not incorporated into proteins.

The name "taurine" originates in the prefix "tauro-", Latin for "bull." Taurine was first isolated from ox bile. One current commercial process for producing taurine involves hydrolysis of the bile acids in ox bile.

In bile, taurine is a part of certain conjugated bile acids. Bile acids are necessary for fat emulsification and digestion. Lack of taurine causes retinal degeneration in cats and in humans deprived of this substance.

2a. The petitioner's name, address and telephone number and other contact information.

The International Formula Council
1100 Johnson Ferry Road NE, Suite 300
Atlanta, GA 30342
Contact: Mardi Mountford, Executive Vice President
Phone: (678) 303-3027
Email: mmountford@kellencompany.com

2b. Manufacturer names, addresses, telephone numbers and other contact information.

USP grade taurine is a standard article of commerce available from many sources. Three recognized suppliers are:

Sogo Pharmaceutical Co., Ltd.
Nippon Bldg., 2 - 6 - 2, Ohtemachi
Chiyoda-Ku, Tokyo, Japan
Tel: +81-3-3279-6891
Fax: +81-3-3279-6630
E-mail: sales-dept@sogo-pharma.co.jp
Website: www.sogo-pharma.co.jp

Qianjiang Yongan Pharmaceutical Co., LTD
No. 16 Zhuze Road
Qianjiang, China
Tel: + 86-728-6202727/6201636
Fax: +86-728-6202797
E-mail: yasales@chinataurine.com
Website: www.chinataurine.com

Changshu Yudong Chemical Company
Wangshi Haiyu Town
Changshu City
Jungshu Province, China PC 215519

Tel +86-512-52565808
Fax +86-512-52561808
E-mail: yonglida@public1.sz.js.cn
Website: www.yudongchem.com

3. Current Use.

Taurine is currently used to fortify conventional infant formulas and infant formulas labeled as "organic" with the nutrient taurine, in accordance with the recommendations of independent professional associations, the European Directive for infant formula and the Codex Alimentarius Commission International Infant Formula Standard CODEX STAN 72-1981. The specific function of taurine is as a "nutrient supplement" [21 CFR 170.3(o)(20)].

4. Handling activities for which the substance is used.

Taurine salts are added to infant formula products to fortify them to the level of taurine supplied by human milk. Infant formulas containing insufficient taurine could result in subpar fat digestion and absorption by infants.

Mode of action:

In the body, taurine is a component of taurocholic acid, an important bile acid. Bile acids are critical for fat digestion and absorption. Half of the calories (food energy) of infant formulas are supplied by fat, so efficient fat digestion and absorption are important to the infant's energy balance. (Human milk supplies approximately half of its calories as fat.)

5. Source of the substances and a detailed description of the manufacturing process.

Taurine was originally isolated from ox bile in 1901 by chemical hydrolysis of conjugated bile acids. Taurine currently is produced synthetically by several different reactions.

Taurine can be made by first reacting ethylene oxide with aqueous sodium bisulfite to form isethionic acid. Isethionic acid is an alkane sulfonic acid that contains a hydroxyl group. The hydroxyl group in isethionic acid is then replaced with an amine group by treatment with ammonia, forming taurine.

Similarly, ethylene chloride can be sulfonated by sodium sulfite, followed by ammonolysis with either anhydrous ammonia or ammonium carbonate to form taurine (Merck 2001)

The process most used in China begins with ethanolamine. Taurine (2-aminoethanesulfonic acid) can be synthesized via reaction of 2-aminoethylsulfuric acid (prepared from monoethanolamine and sulfuric acid) with sodium sulfite. Taurine is separated from the excess of sodium sulfite by extraction with concentrated aqueous ammonia (25%).

6. Summary of any available previous reviews of the petitioned substance.

a. A 2007 Cochrane systematic database review[1] of the publications regarding the effect of taurine supplementation on fat absorption reported these main results:

> Nine small trials were identified. In total, 189 infants participated. Most participants were greater than 30 weeks gestational age at birth and were clinically stable. In eight of the studies, taurine was given enterally with formula milk. Only one small trial assessed parenteral taurine supplementation. **Taurine supplementation increased intestinal fat absorption [weighted mean difference 4.0 (95% confidence interval 1.4, 6.6) percent of intake].** However, meta-analyses did not reveal any statistically significant effects on growth parameters assessed during the neonatal period or until three to four months chronological age [rate of weight gain: weighted mean difference -0.25 (95% confidence interval -1.16, 0.66) grams/kilogram/day; change in length: weighted mean difference 0.37 (95% confidence interval -0.23, 0.98) millimetres/week; change in head circumference: weighted mean difference 0.15 (95% confidence interval -0.19, 0.50) millimeters/week]. There are very limited data on the effect on neonatal mortality or morbidities, and no data on long-term growth or neurological outcomes.

b. Life Sciences Research Office (LSRO), American Societies for Nutritional Sciences. Assessment of Nutrient Requirements for Infant formulas. J Nutr 1998;128(Supp):2059S–2298S. (under contract for the FDA). Page 2060S.

According to the summary of the LSRO report reviewing the nutrients in infant formula, "the specification of a maximum value for . . . taurine . . . , in conjunction with a minimum value of zero, did not constitute an endorsement for the inclusion of that substance; but rather a recognition of apparent safety at levels defined by the maximum. Additional rationale for each nutrient is provided in the 'Conclusions and Recommendations' sections."

This additional rationale reads as follows (p. 2067S):

> *Taurine*
>
> *Minimum*: The Expert Panel found no compelling evidence to mandate the addition of taurine to formulas for term infants. However, the Expert Panel was aware of the history of use of taurine in formulas and the continued presence of taurine in some commercially

[1] Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Verner A, Craig S, McGuire W. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006072.

available formulas. Consequently, the Expert Panel recommended a minimum taurine content of zero.

Maximum: The Expert Panel recommended a maximum taurine content of infant formulas of 12 mg/100 kcal, a value similar to the upper limit reported for human milk.

c. Scientific Committee on Food. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. Brussels, European Commission 2003. SCF/CS/NUT/IF/65 Final 2003.

Page 28:

Taurine is the predominant free amino acid in human milk (4 to 5 mg/100 mL or 0.3 to 0.4 mmol/L) (Agostoni *et al.*, 2000). In infant formula it is only present if added.

Page 35:

Taurine must be added to infant formula based on protein hydrolysates in amounts to achieve at least 5.25 mg/100 kcal (42 μmol/100 kcal) and L-carnitine must be added to infant formulae based on protein hydrolysates and soy protein isolates to achieve a content of at least 1.2 mg/100 kcal (7.5 μmol/100 kcal).

Page 45:

Hydrolysed protein is permitted in the manufacturing of infant formula intended for healthy non-breast-fed infants at risk for atopic diseases. The method and extent of hydrolysis and processing must be documented but are not regulated. The minimum protein level is 2.25 g/100 kcal. The protein content is calculated with a conversion factor of 6.25 and both taurine (42 μmoles/100 kcal) and L-carnitine must be added (7.5 μmoles/100 kcal).

Pages 59-60:

4.7.1 Taurine

Taurine is a non-protein amino acid that is found in most tissues and in human milk at all lactational stages (3.4 to 8.0 mg/100 mL or 5.1 to 11.9 mg/100 kcal). It is practically absent in mature cows' milk (Rassin et al., 1978) and formula based on cows' milk protein and soy protein isolates. It is added to many infant formulae without adverse effects and little evidence of benefit and mostly because it is found in human milk.

It has recognised functions in bile acid conjugation. Other roles of taurine in the scavenging of hypochlorous acid produced by activated neutrophils and macrophages during the respiratory burst (Cunningham et al., 1998), in the detoxification of retinol, iron and xenobiotics and in calcium transport, myocardial contractility, osmotic regulation and in the central nervous system have been shown mostly in in vitro or animal experiments (Gaull,1989). Taurine is found in high concentrations in foetal and neonatal human brain (Sturman, 1988). Infants fed parenterally developed low levels of taurine in plasma and urine and changes in electroretinography which could be corrected by taurine supplementation (Sturman and Chesney, 1995).

> Infants fed a taurine-supplemented (6 mg/100 mL) infant formula with a protein content of 2 g/100 mL (2.9 g/100 kcal) showed the same growth development from 2 to 12 weeks of age as infants breast-fed or receiving the same formula without taurine. However, blood urea nitrogen levels at 12 weeks were significantly lower than in infants fed the taurine-free formula and similar to breast-fed infants, as were the concentrations of indispensable amino acids in plasma and urine (Räihä et al., 1996). The mechanism of this effect is unclear.
>
> As previously noted (in section 4.5.3) if a specified taurine content is considered to be relevant logically this should not be restricted to formula with hydrolysed protein. The Committee considers that the requirement for a minimum content of taurine in formulae manufactured from hydrolysed protein is not necessary.
>
> The Committee proposes that, when added, taurine addition to any type of infant formula should be not exceeding 12 mg/100 kcal.

d. Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group. ESPGHAN Committee on Nutrition. Journal of Pediatric Gastroenterology and Nutrition, 41:584–599 November 2005. Page 596:

> *Taurine*
>
> In line with previous expert consultations, the IEG sees no need for mandatory addition of taurine to infant formulae, but recommends the optional addition in amounts up to 12 mg/100 kcal.

e. The European Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, the current European regulation for infant formula composition, requires that if taurine is added to infant formulae, the amount of taurine shall not be greater than 2.9 mg/100 kJ (12 mg/100 kcal). EC Directive 2006/1/EC of 22 December 2006 positively lists taurine as a permitted amino acid that can be voluntarily added at a level that would be appropriate for the intended particular use by infants.

f. The Pediatric Nutrition Handbook, 6th Edition, published by the Committee on Nutrition, American Academy of Pediatrics, in 2009, page 327:

> Taurine and carnitine are amino acids that serve important and specific functions in the cell but are not incorporated into proteins. They can be synthesized by the body from cysteine and lysine, respectively, and are present in a mixed diet containing proteins of animal origin. The rates of synthesis in infants fed by total parenteral nutrition or receiving synthetic formula devoid of taurine and carnitine may be insufficient to meet all of their needs and necessitate dietary supplementation. Nearly all infant formulas today contain added taurine.

g. A monograph on taurine published in the journal Alternative Medicine Reviews in February, 2001 and a monograph on taurine published in the FEMS (Federation of European Microbiological Societies) Microbiology Letters in August 2003 are attached in Appendix A, to provide a general overview of taurine.

7. Information regarding the regulatory status of taurine.

The FDA allowed taurine supplementation of infant formula in 1984, based on at least a decade of studies that included composition, provisional essentiality, safety, and function in mammals.[2] Since then, commercial infant formulas in the United States have been supplemented with taurine to compensate for the low amounts provided by bovine milk.

Taurine supplementation of infant formula for full-term infants was begun in Europe in 1981 because of retinal abnormalities in infant monkeys deprived of taurine and in patients who were nourished with parenteral nutrition solutions lacking taurine and cysteine.[3]

The FAO/WHO Codex Alimentarius Commission adopted an international standard for infant formula in 1976 and adopted amendments in 1983, 1985, and 1987. They further revised the standard in 2007. CODEX STAN 72-1981 permits a maximum level of 12 mg/100 kcal of taurine in all infant formulas.

Taurine is listed in the U.S. Pharmacopeia. A copy of the USP Reference Standard for taurine is included at Appendix B, along with the specification for taurine supplied by Sogo Pharmaceutical Company.

Taurine is permitted by the FDA, at 21 CFR 573.980, as an additive in the feed of growing chickens. This regulation is available in Appendix B.

8a. The Chemical Abstract Service (CAS) Number of taurine is 107-35-7.

8b. Labels of products that contains the petitioned substance.

See Appendix C.

9. The substance's physical properties and chemical mode of action.

Taurine is a white, crystalline, odorless powder freely soluble in water. It decomposes above 300°C.

Taurine has two major metabolic roles. Taurine is an essential part of the bile acid "taurocholic acid" and other "taurodeoxycholic acid," the body's most effective fat emulsifiers in the intestine. Taurine is also involved in retinal function. Taurine is essential for cats; taurine-deficient cats become blind. Humans depending on total parenteral (intravenous) feeding also experience retina degeneration if taurine is not provided.

[2] MacLean WC Jr, Benson JD. Theory into practice: the incorporation of new knowledge into infant formula. Semin Perinatol. 1989 Apr;13(2):104-11.

[3] Sturman, J. A. & Chesney, R. W. (1995) Taurine in pediatric nutrition. Pediatr. Clin. North Am. 42:879-897.

Taurine is not carcinogenic or mutagenic; see Section 10b.

Taurine may cause eye and skin irritation, as well as respiratory and digestive tract irritation, during handling. Eye and respiratory protection should be used with any powdery ingredient.

Taurine appears to protect against oxidant-induced injury. "Taurine is a semi-essential amino acid and is not incorporated into proteins. In mammalian tissues, taurine is ubiquitous and is the most abundant free amino acid in the heart, retina, skeletal muscle, brain, and leukocytes. In fact, taurine reaches up to 50 mM concentration in leukocytes. **Taurine has been shown to be tissue-protective in many models of oxidant-induced injury.** One possibility is that taurine reacts with hypochlorous acid, produced by the myeloperoxidase pathway, to produce the more stable but less toxic taurine chloramine (Tau-Cl). However, data from several laboratories demonstrate that Tau-Cl is a powerful regulator of inflammation. Specifically, Tau-Cl has been shown to down-regulate the production of pro-inflammatory mediators in both rodent and human leukocytes."[4]

Taurine is a component of bile in virtually all mammalian species. Bile components are excreted in the feces. Consequently, taurine has been a natural part of animal manures for eons, and is broken down by soil bacteria.

10a. Safety information about the substance including a Material Safety Data Sheet (MSDS).

A Material Safety Data Sheet for taurine is attached in Appendix D.

10b. National Institute of Environmental Health Studies Substance Report.

A specific NIEHS report on taurine does not exist, to our knowledge. Taurine was tested in rats in the Carcinogenic Potency Project at the University of California at Berkeley; experimental results in the Carcinogenic Potency Database were negative in both sexes.[5] Taurine was tested in the National Toxicology Program for genetic toxicity and again tested negative.[6] See appendix D for these two reports.

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[4] Schuller-Levis GB and Park E. Taurine: new implications for an old amino acid. FEMS Microbiol Lett. 2003, Sep 26; 226(2):195-202.

[5] http://potency.berkeley.edu/chempages/TAURINE.html . Accessed May 20, 2011.

[6] Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. Salmonella mutagenicity tests. IV. Results from the testing of 300 chemicals. Environ. Molec. Mutagen. Vol. 11 (Suppl 12) (1988) 1-158. http://ntp.niehs.nih.gov/?objectid=BCA57883-123F-7908-7B4AFA9A60964B49. Accessed May 20, 2011.

11. Research information about taurine.

The full discussion of taurine from the LSRO report of 1998, which discusses the pros and cons of taurine addition to infant formula, is shown in Appendix E.

Several clinical trials, but not all, demonstrate a positive effect of taurine supplementation of infant formula on fat absorption, especially in preterm infants.

Taurine supplementation of a premature formula improves fat absorption in preterm infants. Galeano NF, Darling P, Lepage G, Leroy C, Collet S, Giguère R, Roy CC. Pediatr Res. 1987 Jul;22(1):67-71. **Abstract:** The predominance of taurine (Tau) conjugated over glycine conjugated bile acids in infants fed human milk as opposed to those on formulas without added Tau could account for a more complete absorption of fat. Fifteen low birth weight infants were randomized to either Enfamil Premature or to Enfamil Premature added with 40 mumol/dl of Tau and compared to a third group made up of nine low birth weight infants fed their own mother's preterm milk. Formulas and human milk were fed according to tolerance and constituted the sole nutrition for 3 months. A metabolic study was carried out at 3 wk of age and control of growth was done periodically. Urinary Tau excretion (mumol/dl) was very low (p less than 0.001) in the group fed Enfamil Premature (0.3 +/- 0.1) when compared to the values obtained in infants supplemented with Tau (51.6 +/- 12.5) and in those on human milk (36.3 +/- 7.9). Infants supplemented with Tau (92.5 +/- 1.2) had a coefficient of fat absorption which was higher (p less than 0.05) than the unsupplemented group (87.5 +/- 7.9) and comparable to the human milk-fed group (91.6 +/- 1.4). The effect was more pronounced on the saturated fatty acids and varied inversely with their individual water solubility. There was no effect of Tau on nitrogen retention and growth was identical in the three groups. These data show that the addition of Tau to formula had no effect on growth but improved the absorption of fat especially saturated fatty acids which require higher concentrations of bile acids to form mixed micelles.

Effect of taurine on synthesis of neutral and acidic sterols and fat absorption in preterm and full-term infants. Wasserhess P, Becker M, Staab D. Am J Clin Nutr. 1993 Sep;58(3):349-53. **Abstract**: The effect of dietary taurine on the synthesis of neutral and acidic sterols and fat absorption was investigated in 30 newborn children 2 wk after delivery. The infants were divided into five different groups (n = 6 each) according to their gestational age (GA) and weight for GA, and randomly assigned to receive normal formula or formula supplemented with taurine (479 mumol/L). Neutral sterols, acidic sterols, and fatty acids were determined in formulas and feces by gas-liquid chromatography. Only in preterm infants appropriate for GA and small for GA with a mean GA < 33 wk, did taurine supplementation result in lower cholesterol synthesis (-26 +/- 5% and -9 +/- 2%, respectively; P < 0.05) and higher bile acid excretion (100 +/- 35% and 150 +/- 68%, respectively; P < 0.05) and fatty acid absorption (20 +/- 8% and 8 +/- 3%, respectively; P < 0.05). On the basis of these results taurine supplementation is recommended in preterm as well as in small-for-GA neonates < 33 wks of GA who are not on human milk.

Fat absorption in preterm infants fed a taurine-enriched formula. Bijleveld CM, Vonk RJ, Okken A, Fernandes J. Eur J Pediatr. 1987 Mar;146(2):128-30. **Abstract:** An adapted cow's milk infant formula without or with extra taurine (350 mumol/l) was fed to four and five infants, respectively. The infants, born after 28-32 weeks gestation, and initially fed with a starting formula for preterms, were switched to one of the two above-mentioned formulae at approximately the 16th day of life. Each infant was studied during 4 consecutive weeks. The faecal excretion of fat, energy and total bile acids was determined from 3-day stool collections each week. The addition of taurine to the infant formula neither improved the uptake of fat and energy nor changed the faecal bile acid excretion. Growth velocity was similar in both groups of infants. Based on these results there is no rationale for adding taurine to adapted cow's milk infant formula to obtain a better fat absorption.

A 2007 Cochrane systematic database review[7] of the publications regarding the effect of taurine supplementation on fat absorption by infants reported that taurine supplementation significantly increased intestinal fat absorption [weighted mean difference 4.0 (95% confidence interval 1.4, 6.6) percent of intake]. However, meta-analyses did not reveal any statistically significant effects on growth parameters assessed during the neonatal period or until three to four months chronological age.

Dietary taurine intake may explain the benefits of both breast milk and preterm infant formula on neurodevelopment. Wharton et al.[8] found that low plasma neonatal taurine was associated with lower scores on the Bayley mental development index at 18 months and the WISC-R arithmetic subtest at 7 years. These data support the hypothesis that low taurine status in the neonatal period of preterm infants influences later neurodevelopment and that the advantages of breast milk are partly due to taurine. Based on these results, Heird[9] suggested that taurine is a conditionally essential nutrient for preterm infants and that the recommendation on the taurine content of infant formula should be reconsidered. These two papers are included in Appendix E.

12. Petition Justification Statement.

The reason that the FDA allowed taurine supplementation of infant formulas in the United States in 1984 was to compensate for the very low amounts of taurine provided by cows' milk, which is the base for the most infant formulas. Taurine is practically absent from cows' milk. In addition,

[7] Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Verner A, Craig S, McGuire W. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006072.

[8] Low plasma taurine and later neurodevelopment. B. A. Wharton, R. Morley, E. B. Isaacs, A. Lucas. Archives of Diseases in Childhood Neonatal Edition 2004:89:F497-F498.

[9] Taurine in neonatal nutrition – revisited: Recommendations for no minimal taurine content of infant formula should be reconsidered. W. C. Heird. Archives of Diseases in Childhood Neonatal Edition 2004:89:F473-F474.

infant formulas based on soy or on protein hydrolysates contain absolutely no taurine other than deliberately supplemented taurine. The goal of the FDA's allowance was to enable infants not being breast-fed to receive as much taurine as infants who were being breast-fed.

Two lines of evidence support the essentiality of taurine in the diets of newborn infants: animal deficiency models and biochemical responses of infants (primarily preterm) provided taurine-free diets. The absence of taurine has been associated with the development of retinal degeneration in animal models including primates. The highest concentrations of taurine are found in the newborn and neonatal brain and are usually three- to four-times higher than in the mature brain. These data suggest that taurine may play an important role in the developmental process.[10] The report of Wharton et al. (Appendix E) supports this suggestion.

The latest (6th) edition of the Pediatric Nutrition Handbook, published by the American Academy of Pediatrics, has the following statement at page 327:

> Taurine and carnitine are amino acids that serve important and specific functions in the cell but are not incorporated into proteins. They can be synthesized by the body from cysteine and lysine, respectively, and are present in a mixed diet containing proteins of animal origin. The rates of synthesis in infants fed by total parenteral nutrition or receiving synthetic formulas devoid of taurine and carnitine may be insufficient to meet all of their needs and necessitate dietary supplementation. Nearly all infant formulas today contain added taurine.

Taurine can be formed from the amino acid cystine in the body, but the level of the enzyme required for biosynthesis of taurine is very low in the cat and low in humans and primates.

A major physiological role of taurine is as part of certain bile acids, such as taurocholic acid. Bile acids are the body's digestive emulsifiers or 'detergents' that assist in fat digestion and absorption. The conclusion of a recent meta-analysis of clinical trials of taurine[11] in premature infants was that taurine supplementation increased intestinal fat absorption [weighted mean difference 4.0 percent of intake]. Fat represents approximately 50% of the food energy ("calories") in most infant formulas, so loss of undigested fat in the stool should be avoided.

As stated in Item B.1., the name "taurine" originates in the prefix "tauro-", Latin for "bull," and taurine was first isolated from ox bile. Ox bile is not an edible material. Consuming ruminant bile can cause hepatic and renal toxicity[12]. Taurine occurs naturally in protein-rich animal foods, especially in seafood and meat. Natural sources of taurine cited by Budavari[13] are milks other

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[10] Life Sciences Research Office (LSRO), American Societies for Nutritional Sciences. Assessment of Nutrient Requirements for Infant formulas. J Nutr 1998;128(Supp):2059S–2298S.

[11] Cochrane Database Syst Rev. 2007 Oct 17;(4):CD006072. Effect of taurine supplementation on growth and development in preterm or low birth weight infants. Verner A, Craig S, McGuire W.

[12] http://www.cdc.gov/mmwr/preview/mmwrhtml/00044285.htm . Accessed September 6, 2011.

[13] S. Budavari et al., The Merck Index, 12th Edition. Page 1553. 2001.

than that of dairy cows, the lungs and flesh extract of oxen, shark blood, mussels, and oysters. None of these materials are appropriate for inclusion in an infant formula for various reasons, particularly allergen avoidance issues. According to the Reference Handbook for Nutrition and Health Counselors in the WIC and CSF Programs produced by the Food and Nutrition Service of USDA[14], "protein-rich foods are generally introduced to infants between 6 and 8 months old. Protein-rich foods include meat, poultry, eggs, cheese, yogurt, and legumes. . . . Introduction of protein-rich foods earlier than 6 months old may cause hypersensitivity (allergic) reactions."

No substances currently listed at §205.605 and §205.606 contain significant amounts of taurine.

For these reasons, the substance taurine should be included on the National List at §205.605 to permit the production and sale of "organic" infant formula fortified with taurine to the human milk level.

13. Confidential Business Information Statement.

This petition contains no Confidential Business Information.

[14] Infant Nutrition and Feeding. Publication FNS-288, 1993. Page94.

Appendices

Petition for addition to the National List of the substance TAURINE, for use in infant formula products labeled as "organic."

Appendix A – Taurine Monographs

- Alternative Medicine Reviews in February, 2001; 6(1), 78-82.
- Federation of European Microbiological Societies (FEMS) Microbiology Letters; August 2003

Appendix B – Regulation

- USP Reference Standard for taurine
- Specification for USP Taurine supplied by Sogo Pharmaceutical Company
- Taurine regulatory allowance for feed - 21 CFR 573.980

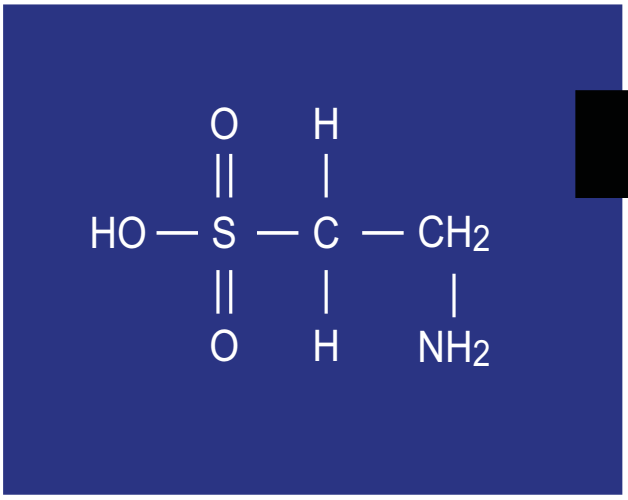
Appendix C – Product Labels

Appendix D

- Taurine National Toxicology Program report
- Taurine Chemical Carcinogenesis Research Information System Report
- Taurine Material Safety Data Sheet (MSDS)

Appendix E

- Taurine discussion – 1998 LSRO report (Pp. 2121S-2122S)
- Low plasma taurine and later neurodevelopment. B. A. Wharton, R. Morley, E. B. Isaacs, A. Lucas. Archives of Diseases in Childhood Neonatal Edition 2004:89:F497-F498.
- Taurine in neonatal nutrition – revisited: Recommendations for no minimal taurine content of infant formula should be reconsidered. W. C. Heird. Archives of Diseases in Childhood Neonatal Edition 2004:89:F473-F474



Monograph

Taurine

Introduction

Taurine is a conditionally essential amino acid that is found in the tissues of most animal species. It is not incorporated into proteins, but is found free in many tissues. Taurine is involved in a number of physiological processes including bile acid conjugation, osmoregulation, detoxification of xenobiotics, cell membrane stabilization, modulation of cellular calcium flux, and modulation of neuronal excitability. Low levels of taurine have been associated with retinal degeneration, growth retardation, and cardiomyopathy. Taurine has been used clinically in the treatment of cardiovascular diseases, hypercholesterolemia, seizure disorders, ocular disorders, diabetes, Alzheimer's disease, hepatic disorders, cystic fibrosis, and alcoholism.

Biochemistry and Biosynthesis

Taurine (2-aminoethanesulfonic acid) is different from other amino acids in that it contains a sulfonic acid group in place of the carboxylic acid group, and it is not incorporated into proteins. Therefore, it is not an amino acid in the true sense of the word.[1] It is synthesized in human liver tissue from cysteine and methionine via three known pathways, all of which require pyridoxal-5'-phosphate, the active coenzyme form of vitamin B6.[2] The highest concentrations of taurine are found in the neutrophil and the retina, and the largest pools of taurine are found in skeletal and cardiac muscles.[3] Taurine excretion is via the urine or in the bile as bile salts.[4]

Physiological Functions

Bile Acid Conjugation

Bile acids, primarily cholic acid and chenodeoxycholic acid, result from cholesterol metabolism in the liver and are involved in emulsification and absorption of lipids and fat-soluble vitamins. In order for this to occur, bile acids must be bound to either glycine or taurine, forming bile salt conjugates. The conjugation of bile acids by taurine results in increased cholesterol solubility and excretion.[5,6]

Detoxification

Research has demonstrated that taurine reacts with and neutralizes hypochlorous acid, which is generated during oxidative neutrophil burst. The result is a stable taurochloramine compound, as opposed to unstable aldehyde compounds formed in states of taurine deficiency. Individuals who are taurine deficient may become more susceptible to tissue damage by xenobiotic agents such as aldehydes, chlorine, and certain amines.[3] Animal studies have also demonstrated taurine's ability to complex with and neutralize the xenobiotic effects of carbon tetrachloride and retinol.[7,8] Research also suggests that translocation of bacterial endotoxins may be a factor in determining a person's response

to xenobiotic insult. Even small amounts of endotoxin markedly enhance liver injury from hepatotoxic substances such as carbon tetrachloride, ethanol, and cadmium. Taurine was found to significantly inhibit intestinal endotoxin translocation and subsequently decrease hepatic injury from these substances.[9,10]

Membrane Stabilization

Taurine's ability to stabilize cell membranes may be attributed to several events. Taurine has been shown to regulate osmotic pressure in the cell, maintain homeostasis of intracellular ions, inhibit phosphorylation of membrane proteins, and prevent lipid peroxidation. As an osmotic regulator, it has been suggested that taurine, along with glutamic acid, is instrumental in the transport of metabolically-generated water from the brain.[11]

Calcium Flux

Taurine is both an intra- and extracellular calcium regulator. Excessive accumulation of intracellular calcium ultimately leads to cell death. Excessive influx of calcium into cells has been demonstrated in various types of myocardial injury, as well as migraines and prolonged epileptic episodes. Taurine supplementation has been shown to be cardioprotective, and of benefit in patients predisposed to epilepsy or migraine.[4,12]

Clinical Indications

Cardiovascular Disease

Several studies indicate taurine is a safe, effective therapeutic tool in the management of various types of cardiovascular disease. Research indicates supplementation with taurine at three to six grams daily for two to three weeks results in reduced serum cholesterol levels in human subjects when compared to placebo.[5,6] In addition, taurine aids in the regulation of intracellular calcium levels, thereby protecting heart muscle from intracellular calcium imbalances, which can lead to cell death, and subsequent myocardial damage.[11] Taurine's use in preventing cardiac arrhythmia is well documented and it is thought it may act by modulating potassium flux in and out of cardiac muscle cells.[13] Research has also shown taurine to be capable of lowering blood pressure, due to its positive inotropic effects.[14,15]

Taurine's antioxidant properties are seen in its ability to inhibit neutrophil burst and subsequent oxidative stress, which can result in reperfusion injury to heart tissue.[16] It is also capable of improving the clinical manifestations of congestive heart failure. A Japanese study revealed taurine was significantly more effective than placebo at decreasing the severity of dyspnea, palpitation, crackles, and edema in congestive heart failure patients, while increasing their capacity for exercise.[17]

Seizure Disorders

A number of studies have been conducted on taurine's role in alleviating seizure conditions. Unfortunately, many had design flaws, dosages varied greatly, and no firm conclusions can be drawn. Some patients with epilepsy have an aberration in taurine and glutamic acid metabolism. It is believed that taurine's anti-epileptic activity is due to its ability to maintain a normal glutamic acid concentration in the central nervous system.[2] As mentioned above, benefits may also be due to taurine's effect on intracellular calcium.[12] It appears however, that taurine's anti-epileptic action is transient and disappears rapidly over a period of a few weeks.[18]

Retinal Degeneration

Taurine is very abundant in the vertebrate retina, and taurine deficiency in cats has been shown to cause damage to the cone photoreceptor cells, resulting in permanent retinal degeneration. It is also thought that abnormalities in taurine metabolism might be associated with retinitis pigmentosa in humans.[1] Retinal taurine appears to regulate osmotic pressure, stabilize cell membranes as well as calcium ion concentrations, inhibit lipid peroxidation after oxidant exposure, and act as an antioxidant by scavenging damaging free radicals.[1,4]

Growth and Development

The research on retinal degeneration in taurine-deficient kittens[1] prompted further studies of taurine deficiency in formula-fed pre-term and full-term infants. Taurine is present in high concentrations in human milk, but significantly decreases over the first few months of the infant's life. Because humans have limited ability to synthesize taurine and infants have decreased capacity to store it, a dietary source of taurine is essential for normal development during the neonatal period.[19] Research on taurine's effects on growth and development in humans shows it may act as a "growth modulator" and that taurine deficiency is responsible for neurological defects involving motor dysfunction and cerebral activity, growth retardation, and retinal degeneration.[4] Animal and *in vitro* studies also support the theory that taurine is essential for proper growth and development. [20,21] As a result, taurine has been added to most commercially-available infant formulas.

Diabetes

Animal and human studies indicate that taurine supplementation is effective in alleviating some of the complications of insulin-dependant diabetes. Taurine has been found to influence blood glucose and insulin levels, as well as increasing glycogen synthesis, and it may also be involved in the functioning and integrity of pancreatic beta cells.[3] In insulin-dependent diabetic patients, both plasma and platelet taurine levels were decreased but were corrected by oral taurine supplementation.[22]

Cystic Fibrosis

Cystic fibrosis is usually characterized by nutrient malabsorption in the ileum, impaired bile acid conjugation, and steatorrhea.[23] Human studies using 30 mg/kg taurine daily for four months resulted in a significant decrease in fecal fatty acids.[23]

Alzheimer's Disease

Low levels of the neurotransmitter acetylcholine and altered taurine metabolism have been found in patients with Alzheimer's disease, and it is thought these abnormalities might contribute to the characteristic memory loss.[4] Also, taurine levels in cerebrospinal fluid were decreased in patients with advanced Alzheimer's disease.[24] To date, no clinical trials of taurine supplementation in patients with Alzheimer's disease have been conducted, but in animal models supplementation increased acetylcholine levels in brain tissue.[25]

Hepatic Disorders

In a double-blind, randomized study, acute hepatitis patients with significantly elevated bilirubin levels were given oral taurine — four grams three times daily after meals. Taurine-supplemented patients exhibited notable decreases in bilirubin, total bile acids, and biliary glycine:taurine ratios within one week when compared to control subjects. The icteric period was also decreased.[26]

In patients undergoing ursodeoxycholic acid (UDC) treatment for cholesterol gallstones, taurine therapy may also be beneficial. The taurine conjugate of UDC is better able to solubilize cholesterol than the glycine conjugate, thereby effecting a greater decrease in the bile acid pool size.[27]

Alcoholism

Both taurine and acamprosate (a synthetic taurine analog) have been shown to be clinically useful in treating patients with alcohol dependence. In patients undergoing alcohol withdrawal, taurine given at one gram three times daily for seven days resulted in significantly fewer psychotic episodes when compared to control subjects.[28] A pooled analysis of 11 studies involving over 3,000 patients given oral acamprosate at similar doses revealed it was more effective than placebo at preventing alcohol relapse. The efficacy appeared to be dose dependent and was enhanced by the addition of disulfiram.[29]

Safety

With few exceptions, animal and human studies have shown taurine administration to be safe, even at higher doses. Intense, temporary itching has been noted to occur in psoriasis patients at dosages of 2 g taurine daily[1] and some epileptic patients reported dosages of 1.5 g daily resulted in nausea, headache, dizziness, and gait disturbances.[30] One study found that taurine administration to patients with uncompensated adrenocortical insufficiency can induce hypothermia and hyperkalemia.[2]

Dosage and Administration

Taurine is usually administered orally, with the adult dosage being 500 mg to 3 g daily in divided doses. Pediatric dosages vary according to the size and age of the child, but range from 250 mg to 1 g daily in divided doses. Patients should be monitored for possible side effects, and taurine administration should be discontinued if serious side effects develop.

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MiniReview

Taurine: new implications for an old amino acid

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Abstract

Taurine is a semi-essential amino acid and is not incorporated into proteins. In mammalian tissues, taurine is ubiquitous and is the most abundant free amino acid in the heart, retina, skeletal muscle, brain, and leukocytes. In fact, taurine reaches up to 50 mM concentration in leukocytes. Taurine has been shown to be tissue-protective in many models of oxidant-induced injury. One possibility is that taurine reacts with hypochlorous acid, produced by the myeloperoxidase pathway, to produce the more stable but less toxic taurine chloramine (Tau-Cl). However, data from several laboratories demonstrate that Tau-Cl is a powerful regulator of inflammation. Specifically, Tau-Cl has been shown to down-regulate the production of pro-inflammatory mediators in both rodent and human leukocytes. Taurolidine, a derivative of taurine, is commonly used in Europe as an adjunctive therapy for various infections as well as for tumor therapy. Recent molecular studies on the function of taurine provide evidence that taurine is a constituent of biologic macromolecules. Specifically, two novel taurine-containing modified uridines have been found in both human and bovine mitochondria. Studies investigating the mechanism of action of Tau-Cl have shown that it inhibits the activation of NF-κB, a potent signal transducer for inflammatory cytokines, by oxidation of IκB-α at Met^{45}. Key enzymes for taurine biosynthesis have recently been cloned. Cysteine sulfinic acid decarboxylase, a rate-limiting enzyme for taurine biosynthesis, has been cloned and sequenced in the mouse, rat and human. Another key enzyme for cysteine metabolism, cysteine dioxygenase (CDO), has also been cloned from rat liver. CDO has a critical role in determining the flux of cysteine between cysteine catabolism/taurine synthesis and glutathione synthesis. Taurine transporter knockout mice show reduced taurine, reduced fertility, and loss of vision due to severe apoptotic retinal degeneration. Apoptosis induced by amino chloramines is a current and important finding since oxidants derived from leukocytes play a key role in killing pathogens. The fundamental importance of taurine in adaptive and acquired immunity will be unveiled using genetic manipulation.

Keywords: Taurine; Taurine chloramine; Inflammatory mediator; Nitric oxide; Tumor necrosis factor α; Cysteine sulfinic acid decarboxylase; Taurolidine

1. Introduction

Taurine, a sulfur-containing amino acid present in high concentrations in mammalian plasma and cells, plays an important role in several essential biological processes such as development of the central nervous system (CNS) and the retina, calcium modulation, membrane stabilization, reproduction, and immunity [1–3]. In fact, taurine is the single most abundant amino acid in leukocytes (20–50 mM) [4]. Taurine, although not incorporated into proteins, is considered to be an essential amino acid for felines and a conditionally indispensable amino acid for humans and non-human primates [2]. The level of cysteine sulfinic acid decarboxylase (CSD), an enzyme required for biosynthesis of taurine, is very low in the cat and low in humans and primates. For this reason, taurine has been added to infant formula as well as to parenteral solutions. Taurine occurs naturally in food, especially in seafood and meat. The mean daily intake from omnivore diets was determined to be around 58 mg. Taurine-containing health drinks, usually containing about 1 g of taurine, are marketed worldwide for the treatment of various conditions, for improvement of athletic performance and for general well being [5]. Animal studies have not indicated toxicity due to taurine. In light of recent evidence on the role of taurine in immunity, risk assessment studies on the effect of these drinks in immunocompromised patients, children, and pregnant women should be performed.

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2. Taurine and taurolidine as adjunct therapy for infections, endotoxemia, and tumors

Several recent papers describe the role of taurolidine (Geislick Pharma, AG, Woljusen, Switzerland) in infection [6]. Taurolidine is a derivative of taurine and is commonly used in Europe, the UK, Ireland and the USA as adjunctive therapy for various infections. Taurolidine is chemically designated as bis-(1,1-dioxyperhydro-1,2,4-thiadiazinyl-4) methane and consists of two taurolidine rings derived from taurine and three molecules of formaldehyde combining to form a two-ringed structure bridged by a methylene group [6]. Taurolidine, which is stable, has a short half-life, is non-toxic, metabolizes to taurine, CO_2 and H_2O, and irreversibly inactivates lipopolysaccharide (LPS). Recent reports include anti-endotoxin, anti-bacterial, and anti-adherence activities for taurolidine. Taurolidine is now included in a new catheter lock solution (Neutrolin; Biolink, Norwell, MA, USA) to prevent catheter-related infections. Bedrosian et al. [7] attribute the activity of taurolidine to blocking the production of interleukin (IL)-1 and tumor necrosis factor (TNF). Taurolidine may have anti-bacterial action that is independent of the resultant taurine metabolites. While both taurine and taurolidine can down-regulate inflammation, it is unclear whether taurine is anti-bacterial and would be useful in a serious infection. Tissue damage could be minimized by taurine's anti-inflammatory properties, but a possible lack of anti-microbial function, associated with enhancement of macrophage and polymorphonuclear leukocyte (PMN) proinflammatory activity, would be detrimental to elimination of pathogens.

In studies by De Costa et al. [8] taurolidine enhanced survival in an animal model of melanoma. Natural killer cells and lymphocyte-activated killer cells were functional in the taurolidine-treated group compared to untreated animals with melanoma, perhaps accounting for the increased survival in the treated group. Taurolidine also inhibited the growth of a rat metastatic colorectal tumor cell line in vitro and in vivo [9]. These studies suggest that taurolidine may have value in management of patients with tumors. Egan et al. [10] have shown in sheep that taurolidine had a therapeutic role in preventing endotoxin-induced lung injury. In this model i.v. taurine (300 mg kg^{-1}), given 1 h before i.v. endotoxin, significantly reduced lung injury.

Although reports of decreased plasma levels of taurine in trauma, sepsis and critical illness are available, very little is known about the relationships among changes in plasma taurine, other amino acid levels, and metabolic variables. A large series of plasma amino acid profiles were obtained in 250 trauma patients with sepsis who were undergoing total parenteral nutrition [11]. The results, which characterized the relationships between plasma taurine and other amino acid levels in sepsis, provide evidence that the more severe decreases in plasma taurine correlate with the worsening of metabolic and cardiorespiratory patterns.

3. Immunologic consequences of taurine deficiency versus supplementation

For cats and primates, deficiency of dietary taurine results in abnormalities in development of the CNS, retinal and tapetal degeneration, as well as significant changes in the cardiovascular and reproductive systems. These changes are also accompanied by abnormalities in the immune system [3]. A lack of taurine in the diet of cats resulted in a significant leukopenia, a shift in the percentage of polymorphonuclear and mononuclear leukocytes, an increase in the absolute count of mononuclear leukocytes, and a change in the sedimentation characteristics of white cells. Functional studies of polymorphonuclear cells isolated from cats fed taurine-free diets demonstrated a significant decrease in the respiratory burst as measured by chemiluminescence as well as a decrease in phagocytosis of *Staphylococcus epidermidis* compared to cats fed the same diet containing taurine. In addition, serum γ-globulin in cats fed taurine-free diets was significantly increased compared to taurine-supplemented cats, indicating that other immune cells may be affected by taurine deficiency. Histological examination of lymph nodes and spleen revealed regression of follicular centers with depletion of reticular cells, mature and immature lymphocytes as well as mild extravascular hemolysis [3]. These results indicate there are profound immunologic abnormalities in cats with prolonged taurine deficiency.

Reports indicate an increased incidence of pediatric problems in children from vegan communities that eat little to no taurine [12]. These problems are usually attributed to malnutrition but a role for immunologic and other consequences of taurine deficiency cannot be ruled out.

Taurine is found in particularly high concentrations in tissues exposed to elevated levels of oxidants. Several in vivo models of oxidant-induced damage have been studied using taurine as a protectant against inflammation. Hamsters pretreated with supplemented dietary taurine and then exposed to NO_2 did not show morphological alterations typical of NO_2 damage [13]. Wang et al. [14] demonstrated that taurine and niacin reduced the inflammation and fibrosis caused by bleomycin. This group also reported that taurine and niacin blocked the bleomycin-induced increased production of nitric oxide in bronchoalveolar lavage fluid, as well as the overexpression of iNOS mRNA and NOS protein in lung tissue [15]. Rats treated with guanidinoethanesulfonate, which is a competitive inhibitor of taurine binding and transport and depletes cellular taurine levels, showed enhanced lung pathology after treatment with both bleomycin and paraquat [16]. Thus, maintenance of tissue taurine levels was critical to the prevention of oxidant-induced lung injury.

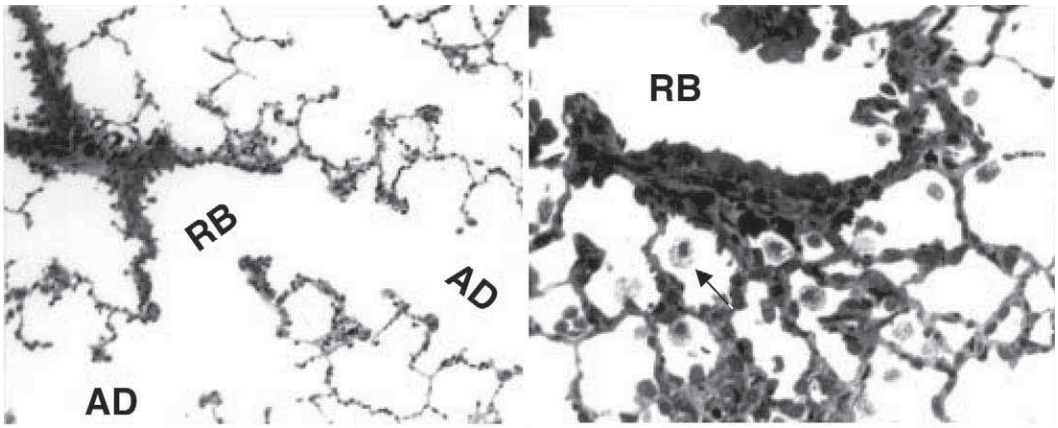

Fig. 1. Left: Light micrograph of rat lung 48 h after ozone exposure (pretreated with taurine). Note that there is no evidence of a macrophage infiltrate. 170×. Right: Light micrograph of rat lung 48 h after ozone exposure (water only). Note many vacuolated macrophages (arrow) present in the alveolar spaces into the respiratory bronchiole (RB), alveolar duct (AD), and surrounding alveoli. 340×.

We performed studies to determine if ozone-induced lung inflammation was modified by pretreatment of 5% taurine in the drinking water for 10 days prior to ozone (O_3) exposure (2 ppm for 3 h). The number of inflammatory cells and hydroxyproline levels in the bronchoalveolar lavage of taurine-treated rats was significantly reduced compared to untreated rats exposed to O_3 [17]. Light microscopy revealed a significant inflammatory infiltrate in the lungs of rats 48 h after exposure to O_3 followed by focal hyperplasia in the terminal and respiratory bronchioles (72 h) (Fig. 1). Rats pretreated with taurine in the drinking water for 10 days and then exposed to O_3 showed none of these alterations (Fig. 1). These results show that supplemental taurine protects rats from acute ozone-induced lung inflammation and hyperplasia.

Bleomycin-induced lung injury results in dysregulated matrix remodeling, leading to thickened alveolar walls, alveolar collapse and scarring [18]. Fibrosis culminates in the overproduction of interstitial collagen. Fibrosis is strikingly absent and inflammation is reduced in the lung of rats pretreated with 5% taurine in the drinking water for 10 days prior to bleomycin instillation [18]. Significantly more intercellular adhesion molecule (ICAM) was demonstrated in the bleomycin-treated group compared to the taurine-treated bleomycin group, indicating that ICAM correlated with lung damage. Those cells which do enter the lung in the taurine-treated group do not appear to 'stick and stay' which may be one mechanism for the absence of fibrosis in this group.

Other evidence supporting the 'stick and stay' idea is the data of Abdih et al. [19] and Egan et al. [20]. Abdih et al. [19] demonstrated that taurine prevents IL-2-induced acute lung injury, in part, by decreasing neutrophil interactions. Data from Egan et al. [20] demonstrate that following administration of LPS there was an increase in leukocyte rolling accompanied by an increase in the num-

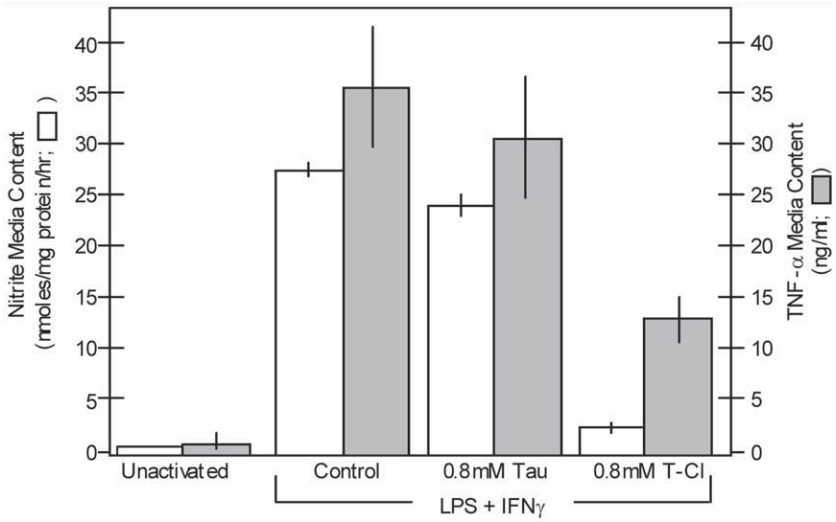

Fig. 2. Tau-Cl inhibits the amount of NO_2^- and TNF-α recovered in the media of LPS- and IFN-γ-activated RAW 264.7 cells. Conditioned medium was collected 16 h after activation and assayed as described in the text. Values represent the mean ± S.D. of triplicate samples. Asterisks indicate a significant difference from control values ($P < 0.05$). Similar results were obtained in six to eight independent experiments. Reprinted from Park et al. [25], ©1995 The American Association of Immunologists, Inc.

ber of adherent leukocytes and transendothelial migration. Taurine given orally as a 4% solution significantly attenuated the LPS-induced leukocyte rolling and attenuated the number of adherent leukocytes as well as the increase in transendothelial cell migration.

Our hypothesis is that supplemental taurine in the drinking water increases the available taurine both systemically and at the site of inflammation. Leukocytes capable of generating hypochlorous acid (HOCl) from hydrogen peroxide (H_2O_2) and chloride via the myeloperoxidase (MPO) pathway have intracellular concentrations of taurine of 20–50 mM. Moreover, in physiologic fluid extracellular taurine concentrations range from 50 to 100 mM after taurine supplementation [21]. Taurine reacts with HOCl to produce the less reactive and long-lived oxidant taurine chloramine (Tau-Cl). Thus, Tau-Cl, a stable oxidant, can be produced at the site of inflammation and down-regulate proinflammatory cytokine production leading to a significant reduction in the immune response. Taurine may provide a useful prophylactic approach to preventing tissue damage resulting from inflammation.

4. Taurine chloramine, the 'active' product of taurine, and the MPO pathway

Neutrophils and monocytes contain high levels of MPO, which, along with H_2O_2, catalyzes the formation of the potent oxidant, HOCl. Taurine, the most abundant free amino acid, scavenges HOCl to form the more stable and less toxic Tau-Cl [22,23].

Tau-Cl inhibits in a dose-dependent manner the production of both NO and TNF-α by activated RAW 264.7 cells, a macrophage-like cell line (Fig. 2) [24]. Tau-Cl (0.8 mM) inhibited secretion of TNF-α into the media and nitrite production from activated RAW 264.7 cells by 65% and 91%, respectively. To examine the mechanism(s) whereby Tau-Cl inhibits inflammatory cytokines, activated cell lysates in the presence or absence of Tau-Cl were analyzed for the inducible form of NO synthase (iNOS) by Western blot analysis, and TNF-α and iNOS mRNAs were assessed by Northern blot analysis [25]. Western blot analysis showed that iNOS protein was absent from cells activated with LPS and rIFN-γ in the presence of 0.8 mM Tau-Cl. Northern blot analysis demonstrated that Tau-Cl (0.8 mM) significantly inhibited iNOS mRNA at all time points examined (Fig. 3) demonstrating that Tau-Cl inhibits transcription of the iNOS gene. In the same experiments, Tau-Cl delayed the peak expression of TNF-α mRNA from 4 h to 8 h, with continuing expression of high TNF-α transcripts after 24 h of activation. TNF-α secreted into the medium was inhibited by the same doses of Tau-Cl used in the Northern blot experiments, indicating that although TNF-α mRNA is present, translation of this message is impaired. The effects of Tau-Cl are not a result of either changes in viability (data not shown) or a generalized effect on gene transcription because α-actin mRNA was intact with treatment of Tau-Cl (see Fig. 3 for increase in TNF-α message).

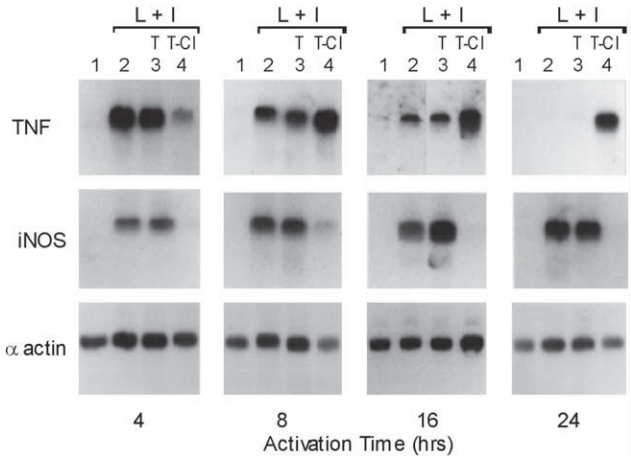

Fig. 3. Kinetics of iNOS, TNF-α and α-actin mRNA expression in RAW 264.7 cells. Cells were obtained 4, 8, 16, and 24 h after activation. Total RNA fractions from cells unactivated in the presence of either 0.8 mM taurine (lane 3) or 0.8 mM Tau-Cl (lane 4) are shown. Similar results were obtained in two to three additional independent experiments. Reprinted from Park et al. [25], ©1995 The American Association of Immunologists, Inc.

Studies on Tau-Cl have been performed using macrophage cell lines and activated murine and rat macrophages. Recent studies have demonstrated that Tau-Cl suppressed superoxide anion, IL-6 and IL-8 production in activated human peripheral blood PMNs [26]. In addition, using both adherent and non-adherent leukocytes, many proinflammatory mediators were significantly decreased by Tau-Cl [27]. Choray et al. have confirmed and extended these finding using LPS-stimulated peripheral blood monocytes from humans [28].

Early administration of Tau-Cl resulted in the delay of the onset of collagen-induced arthritis (CIA) in DBA1/J mice [29]. This is the first study to use Tau-Cl in vivo for immune intervention. An analysis of genes involved in the inflammatory process of joints in DBA1/J mice with CIA was performed using microarrays [30]. Of the 11,000 genes assayed, 223 increased four-fold or more. Nine genes mapped to the chromosome contributing to susceptibility to CIA, including the taurine transporter gene.

Kontny et al. [31] have shown that Tau-Cl inhibits the production of proinflammatory cytokines (IL-6 and IL-8) by fibroblast-like synoviocytes isolated from rheumatoid arthritis patients. In these studies Tau-Cl diminished the activity of NF-κB and to a lesser extent, that of AP-1 transcription factor. This possible mechanism for down-regulation of proinflammatory cytokines was also demonstrated by Barua et al. (see Section 5) [32].

Marcinkiewicz et al. found that treatment of T-cells with Tau-Cl prior to activation inhibited IL-2 release in response to both mitogen and antigenic stimulation [33].

In addition, this group found exposure of dendritic cells to Tau-Cl affected their ability to stimulate T-cell responses. The authors suggest that Tau-Cl may favor the development of a Th_1 rather than a Th_2 response.

5. Recent molecular studies on the function of taurine and its chloramine

Taurine has thus far not been found as a component of a protein or nucleic acid and its precise biochemical mechanism(s) are unclear. Exciting studies from Suzuki et al. [34] demonstrate the first reported evidence taurine is a constituent of biologic macromolecules, which is a significant new insight into the function of taurine. They identified two novel taurine-containing modified uridines (5-taurinomethyluridine and 5-taurinomethyl-2-thiouridine) in human and bovine mitochondrial tRNAs. These nucleotides are synthesized by a direct incorporation of taurine supplied to the medium. They found an absence of taurine modified mitochondrial uridine in the cells from the mitochondrial diseases MELAS and MERRF. These findings will hopefully lead not only to development of therapies for these diseases but to clues for understanding an important biochemical function of taurine.

Barua et al. [32] have demonstrated that Tau-Cl depressed NF-κB migration into the nucleus of activated NR8383 cells, a cloned cell line derived from rat alveolar macrophages, and caused a more sustained presence of IκB in the cytoplasm. In additional experiments, Tau-Cl did not directly inhibit IκB kinase (IKK) activity suggesting that Tau-Cl exerts its effects at some level upstream of IKK in the signaling pathway.

Kanayama et al. [35] report Tau-Cl-induced inhibition of NF-κB activation by the oxidation of IκB-α. Deletion experiments showed that the Tau-Cl modification site causing the band shift is Met^{45}, indicating that Met^{45} oxidation is a molecular mechanism underlying the Tau-Cl-induced inhibition of NF-κB.

6. Genetic studies on CSD, taurine transporter, and CDO

CSD was first identified in the liver as a rate-limiting enzyme in the biosynthesis of taurine. Reymond et al. [36] demonstrated that in addition to liver and kidney, rat brain expressed CSD mRNA. Brain CSD was strictly localized in glial cells, especially astrocytes, introducing a possible role of taurine in astrocyte–neuron interaction. Reymond et al. [36] and Kaisaki et al. [37] reported a sequenced CSD cDNA in the rat (GenBank accession numbers: X94152 and M64755, respectively). Human CSD has been registered in the GenBank (accession number: AF116548). Since the mouse is a good animal model for studies on the role of taurine in the immune system, we cloned murine CSD cDNA and examined the expression

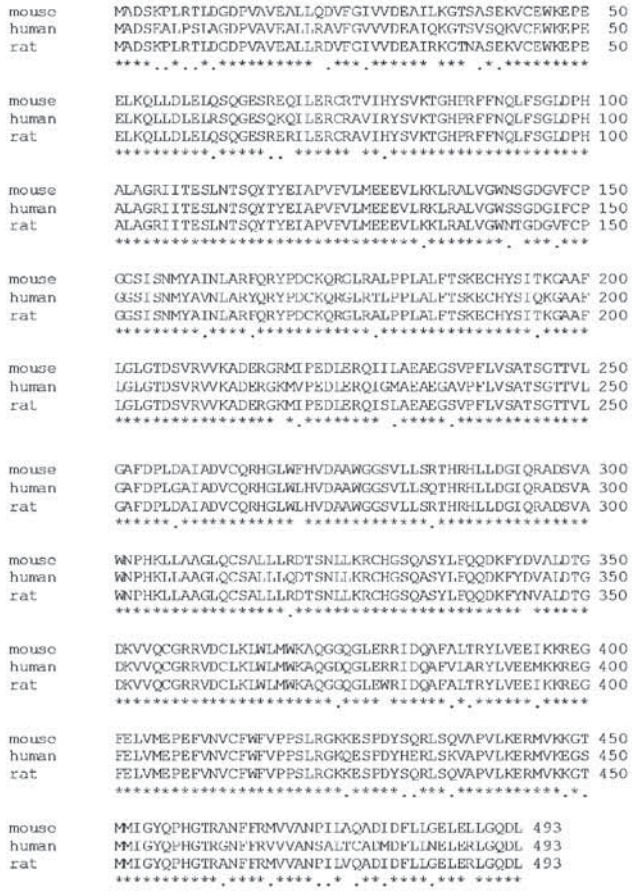

Fig. 4. Amino acid sequence alignment of CSD from mouse, human and rat. An asterisk underneath represents an amino acid conserved in all species whereas a dot represents an amino acid conserved only in mouse and rat. Mouse and human CSDs share 90% amino acid homology whereas mouse and rat CSDs share 98%. Reprinted from Park et al. [38] with permission from Elsevier Science.

of CSD mRNA in various murine tissues including leukocytes. The cDNA sequence of murine CSD, which is a polypeptide of 493 amino acids (Fig. 4) [38], has 98% and 90% sequence homology of amino acids with rat and human CSD, respectively, indicating that it is a true ortholog of CSD. Northern blot analysis revealed that CSD mRNA is expressed in kidney and liver, and was not detected in lymphoid tissues and lung. These data suggest that lymphoid tissue may rely on transport of taurine and may not synthesize taurine directly.

Another key regulatory enzyme for cysteine metabolism is cysteine dioxygenase (CDO, EC 1.13.11.20) cloned from rat liver [39]. The levels of CDO activity changed by dietary protein level, in addition to cysteine availability, are key factors in determining the flux of cysteine between cysteine catabolism/taurine synthesis and glutathione synthesis [40]. Excess sulfur amino acids or protein increase CDO activity and CDO protein but not the levels of mRNA CDO. This suggests that CDO regulation may be posttranslational and possibly involve a decrease in the rate of CDO degradation.

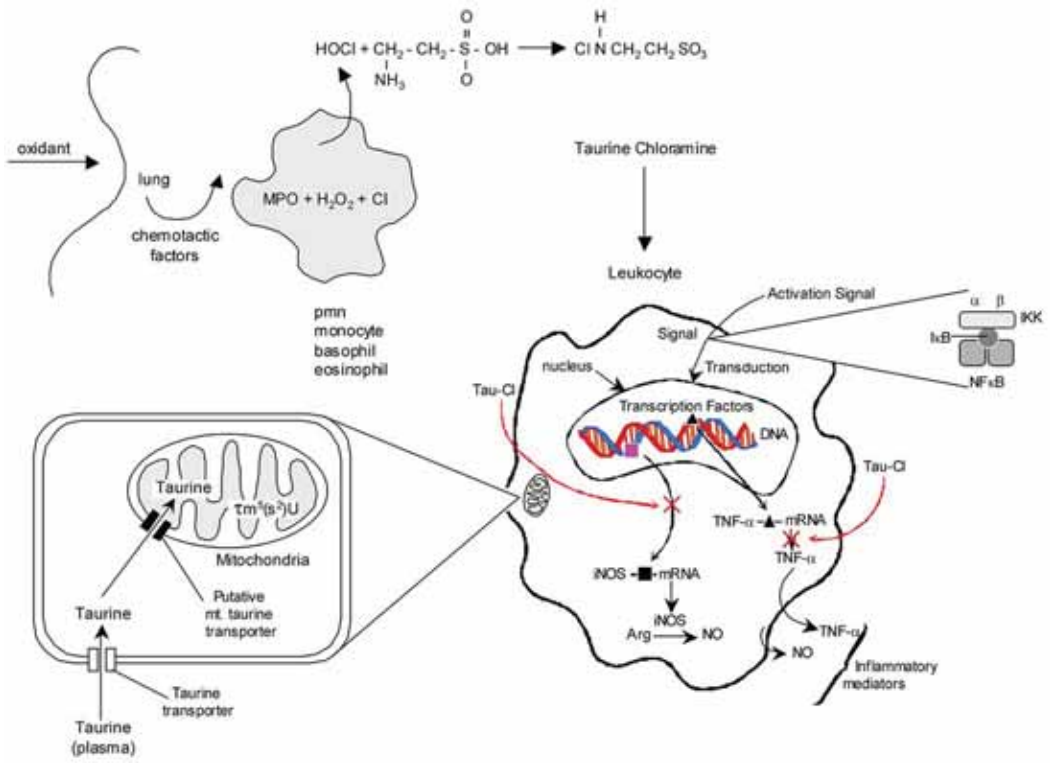

Fig. 5. Schematic representation of formation of Tau-C1 during inflammation, mechanism(s) utilized by Tau-Cl to inhibit production of inflammatory mediators by immune-responsive cells and possible catabolic flow and biosynthetic pathway for mitochondrial taurine. Adapted in part from Suzuki et al. [34] and Quinn and Schuller-Levis [47].

To maintain adequate level of taurine in the tissues, taurine is tightly regulated by excretion and reabsorption by the kidney [41]. The taurine transporter in proximal tubule brush border membranes appears to be the primary target for adaptive regulation by dietary availability of taurine. The genes encoding the taurine transporter (TauT) for various species and tissues share a high degree of homology. TauT gene is located on the central region of mouse chromosome 6 and on human chromosome 3p21–25, where a conserved linkage group of genes has been found between mouse and man [42]. In patients with 3p syndrome, deletion of 3p25–pter is associated with profound growth failure, characteristic facial features, retinal changes and mental retardation, suggesting that deletion of TauT might contribute to some phenotypic features of the 3p syndrome [43].

Heller-Stilb et al. [44] have developed a mouse model with a disrupted gene encoding the taurine transporter (trans−/− mice). These mice show markedly decreased taurine levels in a variety of tissues, reduced fertility, and loss of vision due to severe retinal degeneration. A decrease of taurine concentration by 74% was observed in plasma, kidney, liver, and the eye. In skeletal muscle and heart, taurine levels were decreased by >95%. No data were reported for cells or organs of the immune system. The retinal involvement identifies the taurine transporter as an important factor for the development and maintenance of normal retinal functions and morphology. This progressive retinal degeneration was found to be caused by apoptosis. Han et al. [45] have shown that the taurine transporter gene is a transcriptional target of p53, which functions as a cell cycle checkpoint or may trigger apoptosis in cells with defective genomes. Of particular interest are the findings of Englert et al. [46] which show that amino chloramines induced apoptosis. Using B-cell lymphoma cells, Englert et al. have shown that long-lived aminoacyl chloramines (Tau-Cl being the most abundant) mediate HOCl-induced apoptosis. Since Tau-Cl is formed at the site of inflammation, neutrophil cell death and neutrophil-induced death at the inflammatory site would likely be apoptotic. Apoptotic cell death, in contrast to necrotic cell death, is a physiologic advantage in that cells are cleared by phagocytosis lessening tissue damage. Tau-C1 may promote apoptotic cell death and thereby decrease the detrimental effects of inflammation.

7. Taurine research: new insights

The schematic (Fig. 5) incorporates our findings as well as those of others on the possible mechanism(s) of action of taurine as an immunomodulator and as a component of RNA. Taurine has been shown to be tissue-protective in many models of oxidant-induced injury. Early events in inflammations include migration of leukocytes to the site of injury. These inflammatory cells produce high levels of

HOCl via the MPO pathway and the abundance of taurine assures the production of Tau-Cl. Data show that Tau-Cl can be actively transported into leukocytes and can down-regulate the production of inflammatory mediators. New areas of research should extend these studies to include applications to clinical problems such as autoimmune diseases and inflammation. Two such areas include genetic manipulation of CSD, CDO and TauT which provide an approach to the fundamental roles of taurine in the immune system, CNS, reproduction and osmoregulation, as well as studies on the two novel taurine-containing modified uridines in human and bovine mitochondrial tRNAs.

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umn and about 1.3 mL per minute for a 4.6-mm column. [NOTE—The flow rate can be adjusted as needed to achieve a recommended retention time of tamsulosin at approximately 6 minutes.] Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution between tamsulosin and propylparaben is not less than 12, and the elution order is tamsulosin hydrochloride followed by propylparaben. The relative standard deviation of the ratios of the peak areas for tamsulosin and the internal standard for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area of the major peaks. Calculate the percentage of the labeled amount of tamsulosin hydrochloride ($C_{20}H_{28}N_2O_5S \cdot HCl$) in the portion of Capsules taken by the formula:

$$100 \times (C_S V_S / W)(R_U / R_S)$$

in which C_S is the concentration, in mg per mL, of USP Tamsulosin Hydrochloride RS in the *Standard stock preparation;* V_S is the volume, in mL, of the *Standard stock preparation* taken to prepare the *Standard preparation; W* is the amount of tamsulosin hydrochloride, in mg, based on the label claim, taken to prepare the *Assay preparation;* and R_U and R_S are the ratio of the peak areas for tamsulosin and the internal standard areas obtained from the *Assay preparation* and *Standard preparation,* respectively.

Tannic Acid

Tannin.
Tannic acid; Tannin [*1401-55-4*].

» Tannic Acid is a tannin usually obtained from nutgalls, the excrescences produced on the young twigs of *Quercus infectoria* Oliver, and allied species of *Quercus* Linné (Fam. Fagaceae), from the seed pods of Tara (*Caesalpinia spinosa*), or from the nutgalls or leaves of sumac (any of a genus *Rhus*).

Packaging and storage—Preserve in tight, light-resistant containers.

Identification—

A: To 2 mL of a solution (1 in 10) add 1 drop of ferric chloride TS: a bluish black color or precipitate results.

B: To a solution (1 in 10) add an equal volume of gelatin solution (1 in 100): a precipitate is formed.

Loss on drying ⟨731⟩**—**Dry it at 105° for 2 hours: it loses not more than 12.0% of its weight.

Residue on ignition ⟨281⟩: not more than 1.0%.

Arsenic, *Method II* ⟨211⟩: 3 ppm.

Heavy metals, *Method II* ⟨231⟩: 0.004%.

Gum or dextrin—Dissolve 2 g in 10 mL of hot water: the solution is not more than slightly turbid. Cool, filter, and divide the filtrate into two equal portions. To one portion add 10 mL of alcohol: no turbidity is produced.

Resinous substances—To a portion of the filtrate obtained in the test for *Gum or dextrin* add 10 mL of water: no turbidity is produced.

Adhesive Tape

» Adhesive Tape consists of fabric and/or film evenly coated on one side with a pressure-sensitive, adhesive mixture. Its length is not less than 98.0 percent of that declared on the label, and its average width is not less than 95.0 percent of the declared width. If Adhesive Tape has been rendered sterile, it is protected from contamination by appropriate packaging.

Packaging and storage—Preserve in well-closed containers, and prevent exposure to excessive heat and to sunlight. Tape that has been rendered sterile is so packaged that the sterility of the contents of the package is maintained until the package is opened for use.

Labeling—The package label of Tape that has been rendered sterile indicates that the contents may not be sterile if the package bears evidence of damage or previously has been opened. The package label indicates the length and width of the Tape, and the name of the manufacturer, packer, or distributor.

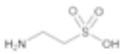
Dimensions—Measure its length: it is not less than 98.0% of the labeled length. Measure its width at 5 locations evenly spaced along the center line of the Tape: the average of 5 measurements is not less than 95% of the labeled width of the Tape.

Tensile strength—Determine the tensile strength of Tape, after previously unrolling and conditioning it for not less than 4 hours in a standard atmosphere of 65 ± 2% relative humidity, at 21 ± 1.1° (70 ± 2°F), with a pendulum-type testing machine, as described under *Tensile Strength* ⟨881⟩. The Tape made from fabric has a tensile strength, determined warpwise, of not less than 20.41 kg (45 pounds) per 2.54 cm of width. The Tape made from film has a tensile strength of not less than 3 kg per 2.54 cm of width.

Adhesive strength—Determine the adhesive strength of Tape that is made from fabric by cutting a strip of the Tape 2.54 cm wide and approximately 15 cm long, and applying 12.90 sq cm, 2.54 cm by 5.08 cm, of one end of the strip to a clean plastic or glass surface by means of a rubber roller under a pressure of 850 g, passing the roller twice over the Tape at a rate of 30 cm per minute. Adjust the temperature of the plastic or glass surface and the Tape to 37°, and conduct the test immediately thereafter as directed under *Tensile Strength* ⟨881⟩, using a pendulum-type testing machine, the pull being exerted parallel with the warp and the plastic or glass surface: the average of not less than 10 tests is not less than 18 kg.

Sterility ⟨71⟩**—**Tape that has been rendered sterile meets the requirements.

Taurine



$C_2H_7NO_3S$ 125.15
Taurine [*107-35-7*].

» Taurine contains not less than 98.5 percent and not more than 101.5 percent of $C_2H_7NO_3S$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—**
USP Taurine RS

Identification, *Infrared Absorption* ⟨197K⟩.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.3% of its weight.

Residue on ignition ⟨281⟩: not more than 0.3%.

Chloride ⟨221⟩—A 0.7-g portion shows no more chloride than corresponds to 0.50 mL of 0.020 N hydrochloric acid. Not more than 0.05% is found.

Sulfate ⟨221⟩—A 0.8-g portion shows no more sulfate than corresponds to 0.25 mL of 0.020 N sulfuric acid. Not more than 0.03% is found.

Iron ⟨241⟩: 0.003%.

Heavy metals, *Method I* ⟨231⟩: 0.0015%.

Chromatographic purity—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve an accurately weighed quantity of Taurine with water to obtain a solution having a concentration of about 10 mg per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Taurine RS with water to obtain a solution having a known concentration of about 0.05 mg per mL, equivalent concentration to about 0.5% of the *Test solution*.

Application volume: 5 µL.

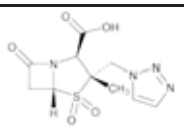
Developing solvent system: a mixture of butyl alcohol, glacial acetic acid, and water (60 : 20 : 20).

Spray reagent—Dissolve 0.2 g ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95 : 5).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩, except to dry the plate at 80° for 30 minutes. Spray the plate with *Spray reagent*, and heat at 80° for about 10 minutes. Examine the plate under white light: no secondary spot in the chromatogram of the *Test solution* is larger or more intense than the principal spot in the chromatogram of the *Standard solution*. Not more than 0.5% of individual impurities are found. [NOTE—The R_F value for the taurine spots should be about 0.2.]

Assay—Proceed as directed for *Method II* under *Nitrogen Determination* ⟨461⟩. Each mL of 0.01 N sulfuric acid is equivalent to 1.25 mg of $C_2H_7NO_3S$.

Tazobactam



$C_{10}H_{12}N_4O_5S$ 300.29

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, [2*S*-(2α,3β,5α)]-.

(2*S*,3*S*,5*R*)-3-Methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide [*89786-04-9*].

» Tazobactam contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}N_4O_5S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩—
USP Endotoxin RS
USP Tazobactam RS
USP Tazobactam Related Compound A RS
(2*S*,3*S*)-2-Amino-3-methyl-3-sulfino-4-(1*H*-1,2,3-triazol-1-yl)butyric acid.
$C_7H_{12}N_4O_4S$ 248.26

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩—The level of Bacterial Endotoxins are such that the requirements under the relevant dosage form monograph(s) in which Tazobactam is used can be met.

Specific rotation ⟨781S⟩**:** between +160° and +167° measured at 20°.

Test solution: 10 mg per mL, in dimethylformamide.

Microbial enumeration tests ⟨61⟩ **and Tests for specified microorganisms** ⟨62⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

pH ⟨791⟩**:** between 1.8 and 2.8, in a solution containing 2.5 mg per mL.

Water, *Method I* ⟨921⟩**:** not more than 0.6%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay*.

Blank—Use *Mobile phase.*

Test solution—Use the *Assay preparation.*

Procedure—Cool and maintain the *Blank* and the *Test solution* at 3° until injection. [NOTE—If an autosampler is used, replace the plastic tubing connected to the injection needle with a stainless steel assembly, and maintain at 3°. If a chilled autosampler is not used, then these solutions should be injected immediately after preparation.] Separately inject equal volumes (about 20 µL) of the *Blank,* and the *Test solution* into the chromatograph; record the chromatograms; and measure the area responses for the peaks. Calculate the percentage of each related compound in the portion of Tazobactam taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response for each related compound in the chromatogram obtained from the *Test solution;* and r_s is the sum of the peak responses of all the peaks in the chromatogram obtained from the *Test solution:* not more than 1.0% of tazobactam related compound A is found; not more than 0.1% of any other individual impurity is found; and the sum of all impurities found, other than tazobactam related compound A, is not greater than 0.3%. [NOTE—Ignore any peaks in the chromatogram of the *Test solution* that correspond to any peaks in the chromatogram of the *Blank*.]

Assay—

Mobile phase—Dissolve 1.32 g of dibasic ammonium phosphate in 750 mL of water. Adjust with 5% (v/v) phosphoric acid to a pH of 2.5, dilute with water to 1000 mL, and mix. Add 30 mL of acetonitrile, mix, and pass through a filter having a 0.2-µm porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Tazobactam RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

System suitability solution—Prepare a solution in *Mobile phase* containing about 0.016 mg of L-phenylalanine, 0.05 mg of USP Tazobactam RS, and 0.008 mg of USP Tazobactam Related Compound A RS per mL. [NOTE—Maintain this solution at 3° until injection. Prepare fresh daily.]

Assay preparation—Transfer about 25 mg of Tazobactam, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1.

2/7

Sogo Pharmaceutical Co.,Ltd.

NIPPON BLDG., 2-6-2 OHTEMACHI,
CHIYODA-KU, TOKYO, JAPAN.
PHONE: 03-3279-6891
FAX: 03-3279-6630
E-mail sales-dept@sogo-pharma.co.jp
URL: http://www.sogo-pharma.co.jp

AMINOETYLSULFONIC ACID

(TAURINE)

$H_2NCH_2CH_2SO_3H$

$C_2H_7NO_3S$: 125.15
CAS NO.107-35-7

Taurine contains not less than 98.5 percent and not more than 101.5 percent of $C_2H_7NO_3S$, calculated on the dried basis.

Packaging and storage — Preserve in well-closed containers.

USP Reference standards 〈11〉 — *USP Taurine RS.*

Identification, *Infrared Absorption 〈197K〉*

Loss on drying 〈731〉 — Dry it at 105° for 3 hours: it loses not more than 0.3% of its weight.

Residue on ignition 〈281〉 : not more than 0.3%

Chloride 〈221〉 — A 0.7-g portion shows no more chloride than corresponds to 0.50 mL of 0.020 N hydrochloric acid. Not more than 0.05% is found.

Sulfate 〈221〉 — A 0.8-g portion shows no more sulfate than corresponds to 0.25 mL of 0.020 N sulfuric acid. Not more than 0.03% is found.

Iron 〈241〉 : 0.003%

Heavy metals, *Method I 〈231〉* : 0.0015%

Chromatographic purity —
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution — Dissolve an accurately weighed quantity of Taurine with water to obtain a solution having a concentration of about 10 mg per mL.

Standard solution — Dissolve an accurately weighed quantity of USP Taurine RS with water to obtain a solution having a known concentration of about 0.05 mg per mL, equivalent concentration to about 0.5% of the Test solution.

Application volume: 5 μL.

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PHONE: 03-3279-6891
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E-mail sales-dept@sogo-pharma.co.jp
URL: http://www.sogo-pharma.co.jp

3/7

Developing solvent system: a mixture of butyl alcohol, glacial acetic acid, and water(60:20:20).

Spray reagent — Dissolve 0.2g ninhydrin in 100mL of a mixture of butyl alcohol and 2 N acetic acid(95:5)

Procedure — Proceed as directed for *Thin-Layer Chromatography* under *Chromatography ⟨621⟩*, except to dry the plate at 80° for 30 minutes. Spray the plate with Spray reagent, and heat at 80° for about 10 minutes. Examine the plate under white light: no secondary spot in the chromatogram of the Test solution is larger or more intense than the principal spot in the chromatogram of the Standard solution. Not more than 0.5% of individual impurities are found. [Note—The R_F value for the taurine spots should be about 0.2.]

Assay — Proceed as directed for *Method II* under *Nitrogen Determination ⟨461⟩*. Each mL of 0.01 N sulfuric acid is equivalent to 1.25mg of $C_2H_7NO_3S$.$_{\%USP26}$

We certify that the quality of this product conform to USP Organic Volatile Impurities requirement.

§ 573.940 Silicon dioxide.

The food additive silicon dioxide may be safely used in animal feed in accordance with the following conditions:

(a) The food additive is manufactured by vapor phase hydrolysis or by other means whereby the particle size is such as to accomplish the intended effect.

(b) It is used or intended for use in feed components as an anticaking agent, and/or grinding aid, as follows:

Feed component	Limitations (percent)
BHT (butylated hydroxytoluene)	2
Methionine hydroxy analog and its calcium salts	1
Piperazine, piperazine salts	0.8
Sodium propionate	1
Urea	1
Vitamins	3

(c) It is used in feed as an anticaking agent in an amount not to exceed that reasonably required to accomplish its intended effect and in no case in an amount to exceed 2 percent by weight of the finished feed.

§ 573.960 Sorbitan monostearate.

The food additive sorbitan monostearate may be safely used alone or in combination with polysorbate 60 as an emulsifier in mineral premixes and dietary supplements for animal feeds.

§ 573.980 Taurine.

The food additive taurine (2-aminoethanesulfonic acid) may be safely used in feed in accordance with the following prescribed conditions:

(a) It is used as a nutritional supplement in the feed of growing chickens.

(b) It is added to complete feeds so that the total taurine content does not exceed 0.054 percent of the feed.

(c) To assure safe use of the additive, the label and labeling shall bear in addition to the other information required by the Act:

(1) The name of the additive.

(2) The quantity of the additive contained therein.

(3) Adequate directions for use.

§ 573.1000 Verxite.

The food additive verxite may be safely used in animal feed in accordance with the following prescribed conditions:

(a) The additive is a magnesium-aluminum-iron silicate conforming to one of the following:

(1)(i) Verxite granules: The additive contains a minimum of 98 percent of hydrobiotite; it is thermally expanded and has a bulk density of from 5 to 9 pounds per cubic foot.

(ii) It is used or intended for use:

(*a*) In poultry feed at a level not to exceed 5 percent of the weight of the finished feed as a nonnutritive bulking agent for restricting calorie intake in pullet replacement feeds.

(*b*) As an anticaking or blending agent, pelleting aid, or nonnutritive carrier for the incorporation of nutrients in poultry, swine, dog, or ruminant feeds, in an amount not to exceed that necessary to accomplish its intended effect and in no case to exceed 1.5 percent of the dog feed or 5 percent of the final feed for other animals.

(2)(i) Verxite flakes: The additive contains a minimum of 98 percent of hydrobiotite; it has a bulk density of from 20 to 30 pounds per cubic foot.

(ii) It is used or intended for use as an anticaking or blending agent in ruminant feeds in an amount not to exceed that necessary to accomplish its intended effect and in no case to exceed 1 percent by weight of the final feed for ruminants.

(3)(i) Verxite grits: The additive contains a minimum of 80 percent of hydrobiotite; it has a bulk density of from 40 to 50 pounds per cubic foot.

(ii) It is used or intended for use as a partial roughage replacement in ruminant feeds in an amount not to exceed that necessary to accomplish its intended effect and in no case to exceed 1 percent by weight of the final feed.

(b) To assure safe use of the additive, the label of any feed additive supplement, feed additive concentrate, feed additive premix, or complete feed prepared therefrom shall bear, in addition to the other information required by the Act, the name of the additive (verxite granules, verxite flakes, or verxite grits), adequate directions for use, and, when the additive is present in excess of 1 percent, a statement of the quantity of the additive contained therein and the term ''nonnutritive'' in juxtaposition therewith.

Similac® formulas for every baby's nutritional needs

Use as directed by your baby's doctor.

Advance	Sensitive	Expert Care
Complete nutrition for the 1st year	For babies with fussiness, gas, & spit-up	For babies needing extra TLC
Advance®	Sensitive	Alimentum®
Organic	Spit-Up	NeoSure®
	Soy	Diarrhea

And **Similac Go & Grow®** for toddlers learning to eat table food

Our **Feeding Expert hotline** is available to help you with feeding questions: **800-986-8800**

SAMPLE UPC 0 70074 59884 0

Breast milk is recommended. If you choose to use infant formula, the makers of Similac have a formula that's right for your baby.

Filled by volume to 1 Quart. Extra space in bottle allows for shaking and easy pouring.

Have product-related questions?
Call 1-800-515-7677,
8:30 am–5:00 pm,
Eastern time, weekdays.
www.Similac.com

#59883 40072 8954-01

Abbott

READY TO FEED — DO NOT ADD WATER

DHA/ARA
BIRTH TO 12 MONTHS
MILK-BASED

BRAND FED #1 IN HOSPITALS

Similac®
ADVANCE®

IMMUNE SUPPORT Early Shield® BRAIN & EYE STRONG BONES
LUTEIN & DHA

USDA ORGANIC
Organic
Complete Nutrition

For Your Baby's 1st Year

Infant Formula with Iron

U-D 1 QT (946 mL)

NUTRIENTS PER 100 CALORIES (5 FL OZ)

PROTEIN	2.07	G	WATER	133	G
FAT	5.40	G	LINOLEIC ACID	860	MG
CARBOHYDRATE	10.9	G			

VITAMINS

VITAMIN A	300	IU	NIACIN	1050	MCG
VITAMIN D	60	IU	FOLIC ACID (FOLACIN)	15	MCG
VITAMIN E	1.5	IU	PANTOTHENIC ACID	450	MCG
VITAMIN K	8	MCG	BIOTIN	4.4	MCG
THIAMIN (VIT. B_1)	100	MCG	VITAMIN C (ASCORBIC ACID)	9	MG
RIBOFLAVIN (VIT. B_2)	150	MCG	CHOLINE	16	MG
VITAMIN B_6	60	MCG	INOSITOL	4.7	MG
VITAMIN B_{12}	0.25	MCG			

MINERALS

CALCIUM	78	MG	COPPER	90	MCG
PHOSPHORUS	42	MG	IODINE	6	MCG
MAGNESIUM	6	MG	SELENIUM	1.8	MCG
IRON	1.8	MG	SODIUM	24	MG
ZINC	0.75	MG	POTASSIUM	106	MG
MANGANESE	5	MCG	CHLORIDE	65	MG

INGREDIENTS: WATER, **ORGANIC** NONFAT MILK, **ORGANIC** MALTODEXTRIN, **ORGANIC** SUGAR, **ORGANIC** HIGH OLEIC SUNFLOWER OIL, **ORGANIC** SOY OIL, **ORGANIC** COCONUT OIL; **LESS THAN 0.5% OF:** C. COHNII OIL*, M. ALPINA OIL†, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, CARRAGEENAN, MAGNESIUM CHLORIDE, SALT, FERROUS SULFATE, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, d-ALPHA-TOCOPHERYL ACETATE, L-CARNITINE, ZINC SULFATE, NIACINAMIDE, CALCIUM PANTOTHENATE, RIBOFLAVIN, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, POTASSIUM IODIDE, SODIUM SELENATE, VITAMIN D_3, CYANOCOBALAMIN, POTASSIUM HYDROXIDE AND NUCLEOTIDES (ADENOSINE 5'-MONOPHOSPHATE, CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)

USE AS DIRECTED BY A DOCTOR
Directions for Preparation and Use

USE BY DATE ON BOTTLE • DO NOT ADD WATER
DO NOT USE IF BAND AROUND CAP OR INNER FOIL SEAL IS DAMAGED.

Your baby's health depends on carefully following these directions. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to boil (sterilize) bottles, nipples and rings before use.

Use

1. **Shake very well before each use**
   Remove protective band; twist off and clean cap
2. **Invert cap; press down to pierce foil, then turn cap a half turn**
   Remove foil
3. **Pour formula into bottle; attach nipple**
   Once feeding begins, use within 1 hour or discard

Prepare and feed all formula in this container within 3 days after opening.

Storage Once opened, store quart bottle in refrigerator. Store prepared bottles in refrigerator and **feed to baby within 48 hours.** Store unopened containers at room temperature; avoid extreme temperatures. Do not reuse container.

Warning Do not use this container to warm formula. **Never use a microwave to warm formula.** Serious burns can result.

Abbott Nutrition, Abbott Laboratories, Columbus, Ohio 43219-3034 USA

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL

NUTRIENTS PER 100 CALORIES (5 FL OZ, PREPARED AS DIRECTED)

PROTEIN	2.07	G	WATER	133	G
FAT	5.63	G	LINOLEIC ACID	860	MG
CARBOHYDRATE	10.4	G			

VITAMINS

VITAMIN A	300	IU	NIACIN	1050	MCG
VITAMIN D	60	IU	FOLIC ACID (FOLACIN)	15	MCG
VITAMIN E	1.5	IU	PANTOTHENIC ACID	450	MCG
VITAMIN K	8	MCG	BIOTIN	4.4	MCG
THIAMIN (VIT. B_1)	100	MCG	VITAMIN C (ASCORBIC ACID)	9	MG
RIBOFLAVIN (VIT. B_2)	150	MCG	CHOLINE	16	MG
VITAMIN B_6	60	MCG	INOSITOL	4.7	MG
VITAMIN B_{12}	0.25	MCG			

MINERALS

CALCIUM	78	MG	COPPER	90	MCG
PHOSPHORUS	42	MG	IODINE	6	MCG
MAGNESIUM	6	MG	SELENIUM	1.8	MCG
IRON	1.8	MG	SODIUM	24	MG
ZINC	0.75	MG	POTASSIUM	105	MG
MANGANESE	5	MCG	CHLORIDE	65	MG

INGREDIENTS: ORGANIC NONFAT MILK, **ORGANIC** MALTODEXTRIN, **ORGANIC** SUGAR, **ORGANIC** HIGH OLEIC SUNFLOWER OIL, **ORGANIC** SOY OIL, **ORGANIC** COCONUT OIL; **LESS THAN 2% OF:** C. COHNII OIL*, M. ALPINA OIL†, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, ASCORBYL PALMITATE, FERROUS SULFATE, SALT, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, MAGNESIUM CHLORIDE, ZINC SULFATE, MIXED TOCOPHEROLS, d-ALPHA-TOCOPHERYL ACETATE, NIACINAMIDE, CALCIUM PANTOTHENATE, L-CARNITINE, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, SODIUM SELENATE, VITAMIN D_3, CYANOCOBALAMIN, POTASSIUM IODIDE, POTASSIUM HYDROXIDE AND NUCLEOTIDES (CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE, ADENOSINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)

Abbott Nutrition, Abbott Laboratories
Columbus, Ohio 43219-3034 USA

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL

USE BY DATE ON CONTAINER • USE AS DIRECTED BY A DOCTOR

Directions for Preparation and Use

Your baby's health depends on carefully following these directions. Proper hygiene, handling and storage are important when preparing infant formula. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to use cooled, boiled water for mixing and if you need to boil (sterilize) bottles, nipples and rings before use.

1. Wash your hands, surfaces and utensils. Pour water into clean bottle (see mixing guide)
2. Add 1 unpacked level scoop (8.6 g) to each 2 fl oz of water. Return dry scoop to holder in lid
3. Cap bottle; shake well; attach nipple. Once feeding begins, use within 1 hour or discard

Storage: Once mixed, store bottles in refrigerator and **feed to baby within 24 hours.** Store unopened or opened container at room temperature; avoid extreme temperatures. **Use opened container contents within 1 month.** Do not reuse container.

Warning: Powdered infant formulas are not sterile and should not be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor. **Never use a microwave to warm formula.** Serious burns can result.

DO NOT USE IF OUTER QUALITY SEAL OR INNER FOIL SEAL IS DAMAGED.

U.S. Patent Nos. 5,700,590; 6,136,858; 6,596,767; 7,090,879; D576,035 and D578,401

POSITION ONLY

0 70074 50822 1

MIXING GUIDE
GUÍA DE MEZCLA

PEEL HERE Despréndase aquí

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. If you choose to supplement breastfeeding with formula or to formula feed exclusively, there is no better formula than Vermont Organics™ ORGANIC Infant Formula DHA and ARA. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**

1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.
Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.
Filled by weight, not by volume. Contents may settle during shipment.
Contents yield approximately 190 fl oz of formula

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.7 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.4 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.1 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (34.8 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (123 g)

Las instrucciones en Español se encuentran al dorso de esta etiqueta

Easy to Digest
Powder • Add Water

Vermont Organics™

For Babies
0-12 Months

organic infant formula with iron

Milk-Based Nutrition

Lipids – DHA & ARA
Nutrients found naturally in mother's milk

- No Antibiotics
- No Added Growth Hormones
- No Potentially Harmful Pesticides

USDA ORGANIC

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** REDUCED MINERALS WHEY, **ORGANIC** VEGETABLE OILS (PALM OR PALM OLEIN, HIGH OLEIC (SAFFLOWER OR SUNFLOWER), COCONUT, SOY), **ORGANIC** NONFAT MILK, **ORGANIC** LACTOSE, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, VITAMIN A PALMITATE, BETA-CAROTENE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (dl-ALPHA TOCOPHERYL ACETATE), MIXED TOCOPHEROL CONCENTRATE, VITAMIN K (PHYTONADIONE), ASCORBYL PALMITATE, THIAMINE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, CYANOCOBALAMIN, NIACINAMIDE, FOLIC ACID, CALCIUM PANTOTHENATE, BIOTIN, ASCORBIC ACID, CHOLINE CHLORIDE, INOSITOL, CALCIUM CHLORIDE, CALCIUM HYDROXIDE, FERROUS SULFATE, ZINC SULFATE, MANGANESE SULFATE, CUPRIC SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM IODIDE, POTASSIUM HYDROXIDE, SODIUM SELENITE, SODIUM CITRATE, TAURINE, SOY LECITHIN, NUCLEOTIDES (ADENOSINE-5'-MONOPHOSPHATE, CYTIDINE-5'-MONOPHOSPHATE, DISODIUM GUANOSINE-5'- MONOPHOSPHATE, DISODIUM INOSINE-5'-MONOPHOSPHATE, DISODIUM URIDINE-5'MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g.	2.2
FAT g.	5.3
CARBOHYDRATE g.	10.6
WATER g.	134
LINOLEIC ACID mg.	750
VITAMINS:	
VITAMIN A IU.	300
VITAMIN D IU.	60
VITAMIN E IU.	2
VITAMIN K mcg.	8
THIAMINE (VITAMIN B1) mcg.	100
RIBOFLAVIN (VITAMIN B2) mcg.	150
VITAMIN B6 mcg.	63
VITAMIN B12 mcg.	0.2
NIACIN mcg.	750
FOLIC ACID (FOLACIN) mcg.	7.5
PANTOTHENIC ACID mcg.	315

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg.	2.3
VITAMIN C (ASCORBIC ACID) mg.	9
CHOLINE mg.	15
INOSITOL mg.	4.1
MINERALS:	
CALCIUM mg.	63
PHOSPHORUS mg.	42
MAGNESIUM mg.	7
IRON mg.	1.8
ZINC mg.	0.75
MANGANESE mcg.	15
COPPER mcg.	71
IODINE mcg.	9
SELENIUM mcg.	2.1
SODIUM mg.	23
POTASSIUM mg.	84
CHLORIDE mg.	56

DISTRIBUTED BY:
VERMONT ORGANICS INFANT FORMULA
147 IND. PARK RD, GEORGIA, VT 05468

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL 02FTP

*A SOURCE OF ARACHIDONIC ACID (ARA)
**A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)

Questions or Comments:
1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

life's DHA•ARA

life's DHA•ARA™ is a trademark of Martek Biosciences Corporation.

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USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, Vermont Organics™ ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ ORGANIC meets all USDA organic certification requirements. In addition to containing sources of organic fat, protein and carbohydrate, Vermont Organics™ ORGANIC is produced without the use of antibiotics, added growth hormones or potentially harmful pesticides.

L19041730-0351

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. This organic soy infant formula powder is free of lactose and cow's milk protein. It is intended to meet the nutritional needs of term infants and babies who are sensitive to lactose or those who do not consume milk protein or milk products. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**

1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.8 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.6 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.4 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (35.2 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (125 g)

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.

Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.

Filled by weight, not by volume. Contents may settle during shipment.

Contents yield approximately 187 fl oz of formula

Martek DHA

Las instrucciones en Español se encuentran al dorso de esta etiqueta

Easy to Digest
Powder • Add Water

Vermont Organics™

For Babies
0-12 Months

soy organic infant formula

with iron

Soy-Based Nutrition

Lipids – DHA & ARA

Nutrients found naturally in mother's milk

- Milk-Free
- Lactose-Free
- No Potentially Harmful Pesticides

USDA ORGANIC

Pareve

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** CORN SYRUP SOLIDS, **ORGANIC** SOY PROTEIN, **ORGANIC** PALM OLEIN OR PALM OIL, **ORGANIC** COCONUT OIL, **ORGANIC** HIGH OLEIC (SAFFLOWER OR SUNFLOWER) OIL, **ORGANIC** SOY OIL, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, ASCORBYL PALMITATE, L-CARNITINE, L-METHIONINE, MIXED TOCOPHEROL CONCENTRATE, SOY LECITHIN, TAURINE, CALCIUM CHLORIDE, CALCIUM PHOSPHATE, CUPRIC SULFATE, FERROUS SULFATE, MAGNESIUM CHLORIDE, MANGANESE SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM CITRATE, POTASSIUM HYDROXIDE, POTASSIUM IODIDE, SODIUM CITRATE, SODIUM SELENITE, ZINC SULFATE, ASCORBIC ACID, BETA-CAROTENE, BIOTIN, CALCIUM PANTOTHENATE, CHOLINE BITARTRATE, CYANOCOBALAMIN, FOLIC ACID, INOSITOL, NIACINAMIDE, PYRIDOXINE HYDROCHLORIDE, RIBOFLAVIN, THIAMINE HYDROCHLORIDE, VITAMIN A PALMITATE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (dl-ALPHA TOCOPHERYL ACETATE), VITAMIN K (PHYTONADIONE).
CONTAINS SOY INGREDIENTS.

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g	2.5
FAT g	5.3
CARBOHYDRATE g	10.6
WATER g	134
LINOLEIC ACID mg	750
VITAMINS:	
VITAMIN A IU	300
VITAMIN D IU	60
VITAMIN E IU	2
VITAMIN K mcg	8
THIAMINE (VITAMIN B_1) mcg	80
RIBOFLAVIN (VITAMIN B_2) mcg	90
VITAMIN B_6 mcg	60
VITAMIN B_{12} mcg	0.3
NIACIN mcg	1000
FOLIC ACID (FOLACIN) mcg	16
PANTOTHENIC ACID mcg	500

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg	3
VITAMIN C (ASCORBIC ACID) mg	12
CHOLINE mg	24
INOSITOL mg	6
MINERALS:	
CALCIUM mg	105
PHOSPHORUS mg	69
MAGNESIUM mg	11
IRON mg	1.8
ZINC mg	1.2
MANGANESE mcg	25
COPPER mcg	75
IODINE mcg	15
SELENIUM mcg	2.8
SODIUM mg	36
POTASSIUM mg	120
CHLORIDE mg	80

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147 IND. PARK RD. GEORGIA, VT 05468

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL 02FTP

* A SOURCE OF ARACHIDONIC ACID (ARA) ** A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)
Ⓟ PAREVE Contains no dairy ingredients. Manufactured on dairy equipment.

Questions or Comments:
1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

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USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, and lactose-sensitivity is a concern, Vermont Organics™ Soy ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ Soy ORGANIC meets all USDA organic certification requirements. A milk-free, lactose-free baby formula containing organic soy protein.

L18A0730-0351

Testing Status of Agents at NTP

L-Taurine

CASRN: 107-35-7

Formula: C2 H7 N O3 S

Synonyms/Common Names:

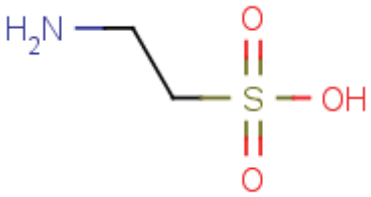
- 2-AMINOETHANESULFONIC ACID (9CI)

Known Uses:

Under investigation as drug for epilepsy.

Genetic Toxicology *(http://ntp.niehs.nih.gov/go/GT)*

- Salmonella (744039) Completed
  - Citation: Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. Salmonella mutagenicity tests. IV. Results from the testing of 300 chemicals Environ. Molec. Mutagen. Vol. 11 (Suppl 12) (1988) 1-158
  - Negative



-TAURINE
CASRN: 107-35-7

For other data, click on the Table of Contents

Substance Identification:

Substance Name: L-TAURINE

CAS Registry Number: 107-35-7

Data Type:
Mutagenicity
Tumor Inhibition

Studies Data:

Mutagenicity Studies:

Test System:	AMES SALMONELLA TYPHIMURIUM
Strain Indicator:	TA100
Metabolic Activation:	NONE
Method:	PREINCUBATION
Dose:	100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results:	NEGATIVE
Reference:	

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Test System:	AMES SALMONELLA TYPHIMURIUM
Strain Indicator:	TA100
Metabolic Activation:	HAMSTER, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method:	PREINCUBATION
Dose:	100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results:	NEGATIVE
Reference:	

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA100
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA1535
Metabolic Activation: NONE
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA1535
Metabolic Activation: HAMSTER, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA1535
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION

Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA97
Metabolic Activation: NONE
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA97
Metabolic Activation: HAMSTER, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA97
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM

Strain Indicator: TA98
Metabolic Activation: NONE
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA98
Metabolic Activation: HAMSTER, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]
Test System: AMES SALMONELLA TYPHIMURIUM
Strain Indicator: TA98
Metabolic Activation: RAT, LIVER, S-9, AROCLOR 1254 (10 OR 30%)
Method: PREINCUBATION
Dose: 100-10000 UG/PLATE (TEST MATERIAL SOLVENT: DMSO)
Results: NEGATIVE
Reference:

[ZEIGER,E, ANDERSON,B, HAWORTH,S, LAWLOR,T AND MORTELMANS,K; SALMONELLA MUTAGENICITY TESTS: IV. RESULTS FROM THE TESTING OF 300 CHEMICALS; ENVIRON. MOL. MUTAGEN. 11(SUPPL.12):1-158, 1988]

Tumor Inhibition Studies:
Species: RAT
Number of Animals Tested: (36,?)/(36,?)
Strain/Sex: F344/MALE
Dose (Inhibitor): 0; 1200 PPM IN DIET BEGINNING 2 WK PRIOR TO CARCINOGEN TREATMENT AND CONTINUING FOR

	DURATION OF STUDY (STUDY DURATION: 56 WK)
Route (Inhibitor):	ORAL
Carcinogen:	AZOXYMETHANE ; 25843-45-2
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	15 MG/KG 1/WK FOR 2 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	COLON: INVASIVE ADENOCARCINOMA
Endpoint (Incidence):	34%, 17%, 50%, NOT SIGNIFICANT
Endpoint (Multiplicity):	0.63, 0.25, 60%, P<0.05
Comments:	BODY WEIGHTS OF AGENT-FED RATS WERE COMPARABLE TO THOSE OF ANIMALS FED CONTROL DIET.

Reference:

[REDDY,BS, RAO,CV, RIVENSON,A AND KELLOFF,G;CHEMOPREVENTION OF COLON CARCINOGENESIS BY ORGANOSULFUR COMPOUNDS; CANCER RES. 53(15):3493-3498, 1993]

Species:	RAT
Number of Animals Tested:	(36,?)/(36,?)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 1200 PPM IN DIET BEGINNING 2 WK PRIOR TO CARCINOGEN TREATMENT AND CONTINUING FOR DURATION OF STUDY (STUDY DURATION: 56 WK)
Route (Inhibitor):	ORAL
Carcinogen:	AZOXYMETHANE ; 25843-45-2
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	15 MG/KG 1/WK FOR 2 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	COLON: NONINVASIVE ADENOCARCINOMA
Endpoint (Incidence):	53%, 47%, 11%, NOT SIGNIFICANT
Endpoint (Multiplicity):	1.03, 0.75, 27%, NOT SIGNIFICANT
Comments:	BODY WEIGHTS OF AGENT-FED RATS WERE COMPARABLE TO THOSE OF ANIMALS FED CONTROL DIET.

Reference:

[REDDY,BS, RAO,CV, RIVENSON,A AND KELLOFF,G;CHEMOPREVENTION OF

COLON CARCINOGENESIS BY ORGANOSULFUR COMPOUNDS; CANCER RES. 53(15):3493-3498, 1993]

Species:	RAT
Number of Animals Tested:	(36,?)/(36,?)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 600 PPM IN DIET BEGINNING 2 WK PRIOR TO CARCINOGEN TREATMENT AND CONTINUING FOR DURATION OF STUDY (STUDY DURATION: 56 WK)
Route (Inhibitor):	ORAL
Carcinogen:	AZOXYMETHANE ; 25843-45-2
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	15 MG/KG 1/WK FOR 2 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	COLON: INVASIVE ADENOCARCINOMA
Endpoint (Incidence):	34%, 16%, 53%, NOT SIGNIFICANT
Endpoint (Multiplicity):	0.63, 0.24, 62%, P<0.05
Comments:	BODY WEIGHTS OF AGENT-FED RATS WERE COMPARABLE TO THOSE OF ANIMALS FED CONTROL DIET.
Reference:	

[REDDY,BS, RAO,CV, RIVENSON,A AND KELLOFF,G;CHEMOPREVENTION OF COLON CARCINOGENESIS BY ORGANOSULFUR COMPOUNDS; CANCER RES. 53(15):3493-3498, 1993]

Species:	RAT
Number of Animals Tested:	(36,?)/(36,?)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 600 PPM IN DIET BEGINNING 2 WK PRIOR TO CARCINOGEN TREATMENT AND CONTINUING FOR DURATION OF STUDY (STUDY DURATION: 56 WK)
Route (Inhibitor):	ORAL
Carcinogen:	AZOXYMETHANE ; 25843-45-2
Route (Carcinogen):	SUBCUTANEOUS
Dose (Carcinogen):	15 MG/KG 1/WK FOR 2 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	COLON: NONINVASIVE ADENOCARCINOMA
Endpoint (Incidence):	53%, 61%, -15%, NOT SIGNIFICANT

Endpoint (Multiplicity):	1.03, 1.03, 0%, NOT SIGNIFICANT
Comments:	BODY WEIGHTS OF AGENT-FED RATS WERE COMPARABLE TO THOSE OF ANIMALS FED CONTROL DIET.
Reference:	

[REDDY,BS, RAO,CV, RIVENSON,A AND KELLOFF,G;CHEMOPREVENTION OF COLON CARCINOGENESIS BY ORGANOSULFUR COMPOUNDS; CANCER RES. 53(15):3493-3498, 1993]

Species:	RAT
Number of Animals Tested:	(20,20)/(20,19)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 3 WK DURING INITIATION PHASE (STUDY DURATION: 24 WK)
Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL
Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	PHENOBARBITAL ; 50-06-6
Route (Promoter):	ORAL
Dose (Promoter):	500 PPM IN DRINKING WATER FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR ADENOMA
Endpoint (Incidence):	19/20 (95%), 12/19 (63%), 34%, P<0.02
Endpoint (Multiplicity):	3.15, 0.95, 70%, P<0.001
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Species:	RAT
Number of Animals Tested:	(20,20)/(20,19)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 3 WK DURING INITIATION PHASE (STUDY DURATION: 24 WK)

Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL
Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	PHENOBARBITAL ; 50-06-6
Route (Promoter):	ORAL
Dose (Promoter):	500 PPM IN DRINKING WATER FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR CARCINOMA
Endpoint (Incidence):	14/20 (70%), 13/19 (68%), 3%, NOT SIGNIFICANT
Endpoint (Multiplicity):	2.00, 1.00, 50%, P<0.05
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Species:	RAT
Number of Animals Tested:	(20,20)/(21,21)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT (STUDY DURATION: 24 WK)
Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL
Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	PHENOBARBITAL ; 50-06-6
Route (Promoter):	ORAL
Dose (Promoter):	500 PPM IN DRINKING WATER FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR ADENOMA
Endpoint (Incidence):	19/20 (95%), 7/21 (33%), 65%, P<0.0001
Endpoint (Multiplicity):	3.15, 0.48, 85%, P<0.0001
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Species:	RAT
Number of Animals Tested:	(20,20)/(21,21)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT (STUDY DURATION: 24 WK)
Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL
Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	PHENOBARBITAL ; 50-06-6
Route (Promoter):	ORAL
Dose (Promoter):	500 PPM IN DRINKING WATER FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR CARCINOMA
Endpoint (Incidence):	14/20 (70%), 13/21 (62%), 11%, NOT SIGNIFICANT
Endpoint (Multiplicity):	2.00, 1.33, 34%, NOT SIGNIFICANT
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Species:	RAT
Number of Animals Tested:	(24,24)/(20,18)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT (STUDY DURATION: 24 WK)
Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL

Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR ADENOMA
Endpoint (Incidence):	3/24 (13%), 4/18 (22%), -69%, NOT SIGNIFICANT
Endpoint (Multiplicity):	0.13, 0.22, -69%, NOT SIGNIFICANT
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Species:	RAT
Number of Animals Tested:	(24,24)/(20,18)
Strain/Sex:	F344/MALE
Dose (Inhibitor):	0; 2000 PPM IN DIET FOR 20 WK BEGINNING POST CARCINOGEN TREATMENT (STUDY DURATION: 24 WK)
Route (Inhibitor):	ORAL
Carcinogen:	DIETHYLNITROSAMINE ; 55-18-5
Route (Carcinogen):	INTRAPERITONEAL
Dose (Carcinogen):	100 MG/KG BW 1/WK FOR 3 WK
Promoter:	NONE USED
Target Tissue: Type of Lesion:	LIVER: HEPATOCELLULAR CARCINOMA
Endpoint (Incidence):	7/24 (29%), 4/18 (22%), 24%, NOT SIGNIFICANT
Endpoint (Multiplicity):	0.38, 0.22, 42%, NOT SIGNIFICANT
Reference:	

[OKAMOTO,K, SUGIE,S, OHNISHI,M, MAKITA,H, KAWAMORI,T, WATANABE,T, TANAKA,T AND MORI,H; CHEMOPREVENTIVE EFFECTS OF TAURINE ON DIETHYLNITROSAMIME AND PHENOBARBITAL-INDUCED HEPATOCARCINOGENESIS IN MALE F344 RATS; JPN. J. CANCER RES. 87(1):30-36, 1996]

Administrative Information:

CCRIS Record Number: 4721

Last Revision Date: 19980429

Update History:
Complete Update on 04/29/1998, 1 field added/edited/deleted.
Complete Update on 03/03/1995, 4 fields added/edited/deleted.
Complete Update on 08/10/1993, 5 fields added/edited/dele

Material Safety Data Sheet

Taurine, 99%

ACC# 94400

Section 1 - Chemical Product and Company Identification

MSDS Name: Taurine, 99%
Catalog Numbers: AC166540000, AC166541000, AC166545000
Synonyms: 2-Aminoethanesulfonic Acid.
Company Identification:

Acros Organics N.V.
One Reagent Lane
Fair Lawn, NJ 07410

For information in North America, call: 800-ACROS-01
For emergencies in the US, call CHEMTREC: 800-424-9300

Section 2 - Composition, Information on Ingredients

CAS#	Chemical Name	Percent	EINECS/ELINCS
107-35-7	Taurine	99%	203-483-8

Hazard Symbols: None listed.
Risk Phrases: None listed.

Section 3 - Hazards Identification

EMERGENCY OVERVIEW

Appearance: white solid. **Caution!** The toxicological properties of this material have not been fully investigated. May cause eye and skin irritation. May cause respiratory and digestive tract irritation.
Target Organs: No data found.

Potential Health Effects

Eye: May cause eye irritation.
Skin: May cause skin irritation.
Ingestion: May cause irritation of the digestive tract. The toxicological properties of this substance have not been fully investigated.
Inhalation: May cause respiratory tract irritation. The toxicological properties of this substance have not been fully investigated.
Chronic: No information found.

Section 4 - First Aid Measures

Eyes: Flush eyes with plenty of water for at least 15 minutes, occasionally lifting the upper and lower eyelids. Get medical aid.
Skin: Get medical aid. Flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Wash clothing before reuse.
Ingestion: Never give anything by mouth to an unconscious person. Get medical aid. Do NOT induce vomiting. If conscious and alert, rinse mouth and drink 2-4 cupfuls of milk or water.

Inhalation: Remove from exposure and move to fresh air immediately. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical aid.
Notes to Physician: Treat symptomatically and supportively.

Section 5 - Fire Fighting Measures

General Information: As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion. Runoff from fire control or dilution water may cause pollution.
Extinguishing Media: In case of fire, use water, dry chemical, chemical foam, or alcohol-resistant foam. Use agent most appropriate to extinguish fire. Use water spray, dry chemical, carbon dioxide, or appropriate foam.
Flash Point: 300 deg C (572.00 deg F)
Autoignition Temperature: Not applicable.
Explosion Limits, Lower: Not available.
Upper: Not available.
NFPA Rating: (estimated) Health: 1; Flammability: 1; Instability: 0

Section 6 - Accidental Release Measures

General Information: Use proper personal protective equipment as indicated in Section 8.
Spills/Leaks: Vacuum or sweep up material and place into a suitable disposal container. Clean up spills immediately, observing precautions in the Protective Equipment section. Avoid generating dusty conditions. Provide ventilation.

Section 7 - Handling and Storage

Handling: Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Use with adequate ventilation. Minimize dust generation and accumulation. Avoid contact with eyes, skin, and clothing. Keep container tightly closed. Avoid ingestion and inhalation.
Storage: Store in a tightly closed container. Store in a cool, dry, well-ventilated area away from incompatible substances.

Section 8 - Exposure Controls, Personal Protection

Engineering Controls: Facilities storing or utilizing this material should be equipped with an eyewash facility and a safety shower. Use adequate ventilation to keep airborne concentrations low.
Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
Taurine	none listed	none listed	none listed

OSHA Vacated PELs: Taurine: No OSHA Vacated PELs are listed for this chemical.
Personal Protective Equipment
Eyes: Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.
Skin: Wear appropriate protective gloves to prevent skin exposure.
Clothing: Wear appropriate protective clothing to prevent skin exposure.

Respirators: Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Always use a NIOSH or European Standard EN 149 approved respirator when necessary.

Section 9 - Physical and Chemical Properties

Physical State: Solid
Appearance: white
Odor: None reported.
pH: Not available.
Vapor Pressure: Not available.
Vapor Density: Not available.
Evaporation Rate: Not available.
Viscosity: Not available.
Boiling Point: Not available.
Freezing/Melting Point:300 deg C
Decomposition Temperature:300 deg C
Solubility: 65 g/l (12 c)
Specific Gravity/Density: Not available.
Molecular Formula:C2H7NO3S
Molecular Weight:125.14

Section 10 - Stability and Reactivity

Chemical Stability: Stable under normal temperatures and pressures.
Conditions to Avoid: Incompatible materials, dust generation, excess heat, strong oxidants.
Incompatibilities with Other Materials: Oxidizing agents.
Hazardous Decomposition Products: Nitrogen oxides, carbon monoxide, oxides of sulfur, irritating and toxic fumes and gases, carbon dioxide, nitrogen.
Hazardous Polymerization: Has not been reported.

Section 11 - Toxicological Information

RTECS#:
CAS# 107-35-7: WX0175000
LD50/LC50:
CAS# 107-35-7:
Oral, mouse: LD50 = >7 gm/kg;
Oral, rat: LD50 = >5 gm/kg;
Carcinogenicity:
CAS# 107-35-7: Not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.
Epidemiology: No information available.
Teratogenicity: No information available.
Reproductive Effects: No information available.
Neurotoxicity: No information available.
Mutagenicity: No information available.
Other Studies: See actual entry in RTECS for complete information.

Section 12 - Ecological Information

No information available.

Section 13 - Disposal Considerations

Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. US EPA guidelines for the classification determination are listed in 40 CFR Parts 261.3. Additionally, waste generators must consult state and local hazardous waste regulations to ensure complete and accurate classification.
RCRA P-Series: None listed.
RCRA U-Series: None listed.

Section 14 - Transport Information

	US DOT	IATA	RID/ADR	IMO	Canada TDG
Shipping Name:	No information available.				No information available.
Hazard Class:					
UN Number:					
Packing Group:					

Section 15 - Regulatory Information

US FEDERAL

TSCA
CAS# 107-35-7 is listed on the TSCA inventory.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b
None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.
SARA

CERCLA Hazardous Substances and corresponding RQs
None of the chemicals in this material have an RQ.
SARA Section 302 Extremely Hazardous Substances
None of the chemicals in this product have a TPQ.
Section 313
No chemicals are reportable under Section 313.
Clean Air Act:
This material does not contain any hazardous air pollutants. This material does not contain any Class 1 Ozone depletors. This material does not contain any Class 2 Ozone depletors.
Clean Water Act:
None of the chemicals in this product are listed as Hazardous Substances under the CWA. None of the chemicals in this product are listed as Priority Pollutants under the CWA. None of the chemicals in this product are listed as Toxic Pollutants under the CWA.
OSHA:
None of the chemicals in this product are considered highly hazardous by OSHA.
STATE

CAS# 107-35-7 is not present on state lists from CA, PA, MN, MA, FL, or NJ.
California No Significant Risk Level: None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives

Hazard Symbols:
Not available.

Risk Phrases:

Safety Phrases:
S 24/25 Avoid contact with skin and eyes.
S 37 Wear suitable gloves.
S 45 In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S 28A After contact with skin, wash immediately with plenty of water.

WGK (Water Danger/Protection)
CAS# 107-35-7: 1

Canada - DSL/NDSL
CAS# 107-35-7 is listed on Canada's DSL List.

Canada - WHMIS
WHMIS: Not available.

Canadian Ingredient Disclosure List

Exposure Limits

Section 16 - Additional Information

MSDS Creation Date: 9/02/1997
Revision #5 Date: 3/18/2003

The information above is believed to be accurate and represents the best information currently available to us. However, we make no warranty of merchantability or any other warranty, express or implied, with respect to such information, and we assume no liability resulting from its use. Users should make their own investigations to determine the suitability of the information for their particular purposes. In no event shall Fisher be liable for any claims, losses, or damages of any third party or for lost profits or any special, indirect, incidental, consequential or exemplary damages, howsoever arising, even if Fisher has been advised of the possibility of such damages.

Additional support for the importance of carnitine in infant nutrition comes from studies of inborn errors of carnitine metabolism. In their review of these disorders, Feller & Rudman (1988) noted that the clinical manifestations are due to disruptions in fatty acid metabolism.

As noted previously, prior to 1986, soybean-based formulas contained less than 2 µmol carnitine/L. Several investigators reported clinical manifestations of carnitine deficiency in infants fed soy-based formulas. These manifestations included failure to thrive, nonketotic hypoglycemia, hypotonia, and cardiomyopathy (Slonim et al., 1981; Winter et al., 1987). Based in part on this evidence, the 1986 revision of the IFA mandated that carnitine be added to soy-based formulas at a level similar to that found in human milk (Penn et al., 1987; Rebouche, 1992).

The focus of studies of carnitine requirements in infants has been on the biochemical response to various dietary interventions, rather than an assessment of endogenous production (Rebouche, 1992). The impact of carnitine supplementation of soy-based formulas on growth and metabolism has been evaluated in several reports (Novak et al., 1983, 1987; Olson & Rebouche, 1989).

Novak et al. (1983) compared two small groups of healthy full-term infants receiving either commercial soy-based formula without carnitine (n=5) or the same formula supplemented with 50 µmol L-carnitine/ml (1.2 mg/100 kcal; n=7), an amount comparable to the levels found in human milk. The test diets served as the sole source of nutrition for the first five months of life. Blood samples were collected monthly throughout the trial and analyzed for free carnitine and lipid metabolites, i.e., free fatty acids, triglycerides, and relative amounts of lipoproteins. Novak et al. (1983) reported lower plasma carnitine levels, higher plasma triglyceride levels, and higher very low density lipoprotein (VLDL) levels in the unsupplemented group. They concluded that their results confirmed the importance of carnitine in fat metabolism and that the absence of a dietary source of carnitine could be metabolically significant. Generalization of the results of this study should be tempered by the small sample size.

In a follow-up study, Novak et al. (1987) compared plasma and urine concentrations of free carnitine and acylcarnitine in three groups of infants (age three- to seven-days-old). One group received a carnitine-free soy-based formula (n=13), and the other two groups received the same formula supplemented with either 50 µmol/ml (1.2 mg/100 kcal; n=13) or 250 µmol/ml (6.0 mg/100 kcal; n=6) of L-carnitine. All infants received a standard cow milk-based formula from birth to the beginning of the trial and the experimental diets until three months of age. Novak et al. (1987) reported that, with the exception of greater concentrations of urine acylcarnitine in the group receiving 250 µmol/ml, no significant differences were found among the three groups at any time during the study.

Olson et al. (1989) compared growth and markers of fat metabolism between infants fed unsupplemented (n=11) and L-carnitine (86 µmol/L; 2.1 mg/100 kcal) supplemented (n = 11) soy-based formula for 112 days. At 56 and 112 days, serum carnitine levels were lower and serum free fatty acids were significantly higher in the unsupplemented group, confirming the Novak et al. (1983) study. The excretion rates of medium-chain dicarboxylic acids were significantly higher in the unsupplemented group although triglyceride levels were similar. No differences in growth rates were observed between these study groups.

Conclusions and recommendations. **The Expert Panel recommended a minimum carnitine content of infant formulas of 1.2 mg/100 kcal (7.5 µmol/100 kcal), a level similar to that found in human milk.** Although the evidence that dietary carnitine is essential for the term infant is not convincing, biochemical changes are noted when infants are fed a carnitine-free diet and there are several anecdotal reports of abnormal clinical manifestations associated with diets low in carnitine. Infants nourished with soy protein-based formula with low carnitine content had lower plasma and urine carnitine levels and evidence of altered lipid metabolism, but no significant differences in rates of growth compared with supplemented infants. The functional significance of these metabolic differences in normal term infants is not known.

The Expert Panel recommended a maximum carnitine content of infant formulas of 2.0 mg/100 kcal (12.4 µmol/100 kcal), a value similar to the upper limit reported for human milk. The Expert Panel was unaware of any studies in which a NOAEL or LOAEL had been identified for carnitine exposure in infants. Consequently, in the absence of data the Expert Panel concluded that the maximum should be set at a level comparable to the upper ranges of carnitine concentrations reported for human milk.

Taurine

Background. Taurine (2-aminoethanesulfonic acid), a small, sulfur-containing β-amino acid with a sulfonic acid group, is an intracellular amino acid found in most tissues. Long considered as simply a by-product of the catabolism of methionine and cysteine, taurine is unique among amino acids in that it is not incorporated into proteins. Numerous biochemical roles have been identified for taurine, including detoxification of retinol, iron and xenobiotics (Emudianughe et al., 1983), calcium transport (Dolara et al., 1973; Huxtable et al., 1980), myocardial contractility (Grosso & Bressler, 1976), and osmotic regulation

(Trachtman et al., 1988a,b). The attention given to taurine relative to its importance in pediatric nutrition is mostly attributable to its well-recognized role in fat digestion via its conjugation with bile acids to form bile salts, and its presumed role in the central nervous system based on data from animal studies (Sturman & Chesney, 1995).

Human milk concentrations of taurine have been reported in the range of 34 to 80 mg/L (5.1 to 11.9 mg/100 kcal)(Harzer et al., 1984; Rana & Sanders, 1986; Rassin et al., 1978), while bovine milk has very low taurine levels. In 1981, supplementation of term infant formula began in European communities, based on experimental evidence and clinical features of deficiency in patients who were nourished only with parenteral nutrition devoid of taurine (Sturman & Chesney, 1995). Since the FDA approval for supplementation in 1984, commercial infant formulas manufactured in the United States have been supplemented with taurine to compensate for the low amounts provided by bovine milk.

Review of extant data. Two lines of evidence support the essentiality of taurine in the diets of newborn infants: animal deficiency models and biochemical responses of infants (primarily preterm) provided taurine-free diets. The absence of taurine has been associated with the development of retinal degeneration in animal models including primates (Imaki et al., 1987; Neuringer & Sturman, 1987; Sturman et al., 1984). Sturman (1988) reported that the highest concentrations of taurine are found in the newborn and neonatal brain and are usually three- to four-times higher than in the mature brain. These data suggest that taurine may play an important role in the developmental process.

Most of the clinical studies involving taurine in humans have been performed in preterm infants (Sturman & Chesney, 1995). One exception was the study by Järvenpää et al. (1983), in which the amino acid profiles of plasma and urine were evaluated in term infants fed diets of taurine-free cow milk formula. Decreased levels of taurine were found in the plasma and urine of infants fed taurine-free formula.

Heird et al. (1987) reported that taurine supplementation during the administration of total parenteral nutrition may reduce the incidence and degree of cholestasis (impairment of bile secretion) in infants. Aside from this report, the Expert Panel was unable to find any additional studies conducted since 1985 which have evaluated the nutritional or toxicological aspects of taurine in term infants.

Conclusions and recommendations. **The Expert Panel found no compelling evidence to mandate the addition of taurine to formulas for term infants. However, the Expert Panel was aware of the history of use of taurine in formulas and the continued presence of taurine in some commercially available formulas. Consequently, the Expert Panel recommended a minimum taurine content of zero.**

The Expert Panel recommended a maximum taurine content of infant formulas of 12 mg/100 kcal, a value similar to the upper limit reported for human milk.

Nucleotides

Background. Nucleotides and their precursors are low-molecular-weight compounds that represent a small component of the nonprotein nitrogen portion of the human diet. The major nucleotides are the pyrimidine bases cytosine, thymine, and uracil, and the purine bases, adenine and guanine, to which a phosphorylated pentose sugar moiety is attached resulting in cytidine monophosphate (CMP), thymidine monophosphate (TMP), uridine monophosphate (UMP), adenine monophosphate (ADP) and guanosine monophosphate (GMP), respectively. Nucleosides are precursors to nucleotides and represent the pyrimidine or purine bases with the unphosphorylated pentose sugar only. The nucleotides function as precursors for the synthesis of the nucleic acids (ribonucleic acid;RNA and deoxyribonucleic acids; DNA) and are also fundamental to cell metabolism. Typically, nucleotides in mammalian cells are generated by *de novo* synthesis from amino acids or by the salvage pathway in which purine and pyrimidine products of protein catabolism are reutilized. These compounds exist in human milk as nucleosides, nucleotides, and nucleic acids. Human milk purine and pyrimidine bases are primarily in the form of nucleic acids.

The total free and cellular nucleotides content of human milk has been estimated to be as much as 20% of the nonprotein nitrogen (Uauy, 1989). According to values cited by Atkinson & Lönnerdal (1995), the RNA concentrations of human milk (100 to 5600 mg/L; 15 to 836 mg/100 kcal) are higher than those of DNA (10 to 120 mg/L; 1.5 to 18 mg/100 kcal). György (1971) observed that the nucleic acid levels of human milk are higher than those of cow milk. The source of nucleic acids in milk is unknown (Atkinson & Lönnerdal, 1995).

A wide range of values has been reported for each of the 13 nucleotide compounds that have been isolated from human milk. Uauy (1989) included a range of about 3 to 11 mg nucleotides/100 kcal in human milk (based on data of mean nucleotide concentrations of pooled milk samples collected 1 to 12 weeks postpartum). Carver & Walker (1995) summarizing data from nine reports, cited a range of 4 to 70 mg/L (0.59 to 10.4 mg/100 kcal) in their recent review of the literature on nucleotides. In two studies of human milk from European women, mean values of total

HYPOTHESIS

Low plasma taurine and later neurodevelopment

B A Wharton, R Morley, E B Isaacs, T J Cole, A Lucas

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Dietary taurine intake may explain the benefits of both breast milk and preterm formula to neurodevelopment. Low plasma neonatal taurine was associated with lower scores on the Bayley mental development index at 18 months and the WISC-R arithmetic subtest at 7 years. Currently it is not mandatory to add taurine to infant formulas.

Preterm babies born in 1982–1985, randomly assigned to a standard formula designed for term babies, subsequently had lower developmental scores than those receiving a multinutrient enriched preterm formula. Yet, paradoxically, infants randomly assigned donated banked breast milk or the same preterm formula had similar scores, despite the lower macronutrient content of human milk.[1–3]

Consideration of the nutrient content of the feeds suggested that taurine was a candidate single nutrient to explain this paradox as term formula contained only a trace, whereas preterm formula and breast milk contained 5 µmol/100 ml (table 1). Furthermore, as taurine is neurotrophic and affects neurotransmission,[4] the possible explanation was biologically plausible. We therefore explored the hypothesis that taurine was an explanatory nutrient for the benefits of both breast milk and the higher nutrient formula to long term neurodevelopment.

PATIENTS AND METHODS

Neonatal plasma taurine concentrations,[5] Bayley Scales of Infant Development (corrected for gestational age) at 18 months of age, and the Wechsler Intelligence Scale for Children-revised (WISC-R) at 7 years were available in 157 children (mean (SD) birth weight, 1398 (277) g; gestation, 31 (2.4) weeks). The lowest (minimum) plasma taurine concentration during their hospital stay was obtained for each subject.

RESULTS

Minimum plasma taurine concentrations correlated with corrected Bayley mental development index ($r = 0.28$, $p < 0.001$) and WISC-R arithmetic subtest score ($r = 0.22$, $p = 0.006$) (fig 1).

These relations remained significant after adjustment for possible confounding factors: (*a*) clinical illness—birth weight, gestational age, weight for gestation, days inpatient, days ventilated; (*b*) possible undernutrition—plasma concentrations of other amino acids, total protein, urea; (*c*) amount of intravenous amino acids.

Minimum taurine was not related to the Bayley psychomotor development nor, after the confounding factors had been allowed for, to the other subtests of the WISC-R. Neither maximum nor mean taurine measurements were related to neurodevelopment.

The length of hospital stay also contributed to lower mental development scores, and gestational age to the WISC-R arithmetic scores. After these factors had been allowed for, the relations of minimum taurine to mental development and to the arithmetic subtest remained significant (partial correlations: $r = 0.19$, $p = 0.016$; $r = 0.18$, $p = 0.024$). There was no interaction between minimum taurine and hospital stay or gestation.

The positive association of neurodevelopment with own mother's milk, described previously, was no longer significant after taurine had been allowed for (partial correlations with mental development: $r = 0.03$, $p = 0.70$; with the arithmetic subtest: $r = 0.09$, $p = 0.24$).

DISCUSSION

The results support the hypothesis that low taurine status in the neonatal period of preterm babies adversely influences later neurodevelopment, and that the advantages of breast milk are partly due to taurine. Some caution is necessary. This was not a randomised trial. The strengths of the relations, although significant, were modest ($r = 0.28$, 0.22), but greater than those seen in this study between either Bayley mental development or the arithmetic subtest of WISC-R with birth weight ($r = 0.17$, 0.18) or gestational age ($r = 0.16$, 0.19).

These data support the view that taurine is a conditionally essential nutrient, as a dietary supply was required for optimum outcome. It is one more example of short term nutritional differences in the newborn having apparent long term effects.

The relations of taurine to mental rather than motor development, and to arithmetic but not other WISC-R subtests, indicate that transiently low neonatal taurine status (''hypotaurinaemia'') has selective neurodevelopmental effects. Transiently low blood concentrations of other metabolic factors have been shown by us and others to be associated with subsequent reduced developmental scores,

Table 1 Nutrient content of breast milk and preterm and term formulas

Energy or nutrients/100 ml	Breast milk*	Preterm formula†	Term formula†
Energy (kcal)	70	80	68
Protein (g)	1.3	2‡	1.5‡
Fat (g)	4.2	4.9§	3.8§
Carbohydrate (g)	7	7.0¶	7.0**
Taurine (µmol)	4.8	5.1	Trace

*Based on analysis of national sample of expressed milk in the United Kingdom.
†Manufacturer's information.
‡Casein to whey ratio 40:60.
§Same fat blend. Saturated to unsaturated ratio 40:60, long chain polyunsaturated fatty acids were not added at time of this trial.
¶Lactose 6 g, maltodextrin 1 g.
**Lactose.
Generally the preterm formula contained a greater concentration of vitamins and minerals except for iron: preterm formula, 40 µg per 100 ml; term formula, 650 µg per 100 ml (all infants received additional iron).

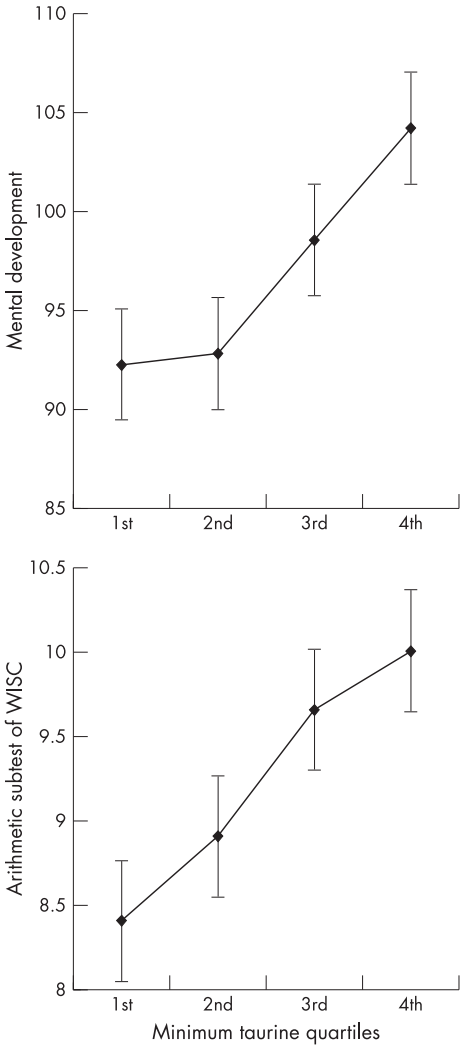

Figure 1 Bayley mental development index at 18 months, arithmetic subtest of WISC-R at 7 years, and minimum neonatal plasma taurine concentration (μmol/l). Taurine, 1st quartile, 20–43; 2nd quartile, 44–55; 3rd quartile, 56–67; 4th quartile, 68–180. Mental development index, mean (SE) 97 (2). Arithmetic score, mean (SE) 9 (0.3).

notably hypoglycaemia and low thyroid hormone status. The mechanisms for this selection are not known, but there are different concentrations of taurine in different parts of the brain. The selective effects of such early influences on brain function require further study. Other work from this centre has shown that calculation deficits are associated with decreased grey matter in the left parietal cortex, and it may be that taurine is implicated in development and function in this region of the brain.[6] Therefore more detailed cognitive testing and neuroimaging studies using magnetic resonance imaging are planned as the children get older.

Although further work is needed to test whether taurine is a conditionally essential nutrient for neurodevelopment in healthy term as well as preterm infants, it seems prudent to ensure adequate early taurine intake. Yet, currently, it is not mandatory to add taurine to infant formulas.

ACKNOWLEDGEMENTS

Ethical approval was given by the local ethical committees at the participating centres. Mothers of the children studied gave informed written consent.

Contributors: BAW was involved in formulating the hypothesis, analysis of results, and initial write up. RM organised and analysed the Bayley and WISC tests. EBI helped in the results analysis and advised on psychology interpretation. TJC gave statistical advice. AL set up the original nutritional intervention trials and the continuing investigation of the children involved. All authors have contributed to, read, and approved the manuscript. AL is guarantor.

Authors' affiliations

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Conflict of interest: BAW has advised the UK Department of Health, European Union, WHO and food companies on various aspects of child nutrition including taurine. Fees for advice/opinions on nutritional child health have been received from WHO and food companies. AL has advised government departments, professional bodies, and industry in the field of nutrition.

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conclusion must be tempered by several methodological concerns. Multiple interventions were applied during the study, and the exact timing and interaction of these interventions are unclear. Some discussion of the background and expertise of the pharmacists participating in the intervention would have been valuable as neonatal expertise and experience are almost certainly important. Unfortunately, the authors expressed the major outcome measure as the absolute number of medication errors, rather than error rates per number of patient days or per number of orders written. We hope that these important denominators remained relatively stable during the study period. In addition, it is unclear to what extent the ascertainment methods used, which relied on voluntary reporting by clinicians, were accurate and unbiased. Voluntary reporting, although valuable on many levels, cannot be relied on to provide accurate incidence data. Finally, the authors provide no statistical measures of differences between the periods before and after intervention.

Implementation of CPOE in the NICU presents special challenges. Systems designed for use in older patients may not adequately address the unique aspects of NICU medication ordering. Unfortunately, development of systems appropriate for use in paediatric and neonatal patients has lagged. Industry must be challenged to provide software applications that are appropriate for NICUs. CPOE almost certainly will have to be integrated with other hospital clinical information systems to have maximum impact on error prevention. Adequate, built in decision support, using population specific knowledge bases, is essential for detecting drug interactions, out of range doses, and other prescribing problems. The LeapFrog Group,[15] a consortium of Fortune 500 companies, has urged hospitals in the United States to adopt CPOE. Given Leapfrog's leverage and influence, recognition of the unique needs of NICUs would be welcome.

Where CPOE is not available, attention to good prescribing practices and accurate communication are essential.[5 16] This is true not only for written orders, but verbal ones as well. The process for verbal orders should include a system of ''read back'' verification to ensure accuracy. Lacking CPOE, clinicians (doctors, nurses, and pharmacists) must implement unambiguous guidelines on appropriate dosing for NICU patients. Good communication and teamwork requires a blame free environment and a culture that places a high value on reporting and discussing patient safety concerns and systems problems.

Finally, NICU clinicians must remain aware of the advances in patient safety made in other industries. Crew Resource Management, which has been pivotal to improving the safety record of the aviation industry, may be particularly useful in helping teams communicate effectively and safely.[17] Translation of technologies from the retail sector, such as bar coding and radio frequency identification, may be helpful in preventing patient misidentification. When feasible, engineering approaches using affordances and reminders, forcing functions, and constraints may help staff to avoid errors due to human factors. Of course, these novel approaches to creating a safe care environment will have to be tailored to the very special and challenging environment of the NICU.

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Neonatal nutrition

Taurine in neonatal nutrition – revisited

W C Heird

Recommendations for no minimal taurine content of infant formulas should be reconsidered.

Taurine (2-aminoethanesulphonic acid) was isolated from ox (*Bos taurus*) bile in 1827[1] but, until the mid to late 1970s, it was thought to be merely a byproduct of sulphur amino acid metabolism. In 1975, it was noted that taurine deficiency in cats was associated with retinal degeneration, which was reversed by taurine supplementation.[2] This observation coupled with the high concentration of taurine in the developing brain[3] and mature retina[4] raised suspicion that taurine may play an important role in brain development. This was supported by observations that brain taurine concentration of several species decreased during the weaning period[3] and that taurine was the primary free amino acid in the milk of most mammals, including humans.[5] Moreover, labelled taurine injected intraperitoneally into lactating rats was found in the milk

of the dam as well as the brain of the suckling pups,[6] suggesting that adequate intake of taurine was important for maintaining brain taurine content.

Shortly after the observation that taurine deficiency in cats resulted in retinal degeneration, evidence that taurine may be a conditionally essential nutrient for the human infant began appearing. The first such evidence came from a study in Scandinavia showing that plasma and urinary taurine concentrations of formula fed infants were lower than those of infants fed human milk,[7] whereas the plasma and urinary concentrations of all other amino acids were higher in formula fed infants.[8 9] This was attributed to the presence of taurine in human milk but not formulas. Subsequently, it was shown that prolonged taurine-free parenteral nutrition resulted in retinal degeneration that was reversed with taurine supplementation.[10] Retinal abnormalities were also found in primates fed a taurine-free infant formula.[11]

On the basis of these findings, taurine was added to most infant formulas by the early to mid 1980s. The only randomised controlled trial of taurine supplementation was started before its routine addition to formulas but terminated for ethical reasons after 37 rather than the planned 50 infants were enrolled. Nonetheless, preterm infants assigned to the taurine supplemented formula had a more mature auditory brain stem evoked response than those assigned to the taurine-free formula.[12] However, no differences in electroretinograms or Brazelton scores were detected. Infants fed taurine supplemented formulas also have a bile salt conjugation pattern more like that of breast fed infants as well as a larger bile salt pool, but reported effects on fat absorption have been mixed.[13–15]

Owing to the relative lack of evidence that taurine supplementation of infant formulas has beneficial clinical effects, recent recommendations for the nutrient contents of term infant formulas do not include a minimum content of taurine.[16] However, as formulas have contained taurine for almost two decades and these seem to be well tolerated, a maximum amount (12 mg/100 kcal) is specified. This is near the maximum content observed in human milk and about 25% more than the content of modern formulas. A minimum content of taurine (5 mg/100 kcal) is specified for preterm infant formulas but without much enthusiasm.[17]

The findings of Wharton *et al*,[18] reported in this issue, suggest that the recommendations for taurine content of infant formulas should be reconsidered. These findings suggest that low plasma taurine concentration during the hospital stay may explain the paradox of higher developmental scores at 18 months[19] and 7 years of age[20] in preterm infants assigned to a nutrient enriched compared with a term formula during initial hospital admission but similar scores in infants assigned to banked human milk compared with the nutrient enriched formula despite the fact that the nutrient density of the banked human milk was even lower than that of the term formula.[21] Although the possibility that the paradoxical neurodevelopmental outcomes were related to taurine intake during infancy was suggested in reviews by Sturman and Chesney in 1995[22] and Chesney *et al* in 1998,[23] Wharton *et al*[18] provide the first indication that this explanation may be valid. They show that the Bayley mental developmental index at 18 months of age and the WISC-R arithmetic subtest score at 7 years of age are correlated with plasma taurine concentrations during infancy. They also report that the positive association of neurodevelopment with own mother' milk[24] was not significant after plasma taurine concentration had been allowed for. These findings are attributed to the presence of taurine in the preterm formula and human milk but not in the term formula.

As the authors emphasise, these findings are far from robust. Firstly, they are not derived from a randomised, controlled trial but, rather, from a retrospective analysis of existing data. Secondly, the strength of the reported relations is modest ($r = 0.28$ and 0.22). Nonetheless, they support the hypothesis that low neonatal taurine status adversely affects later neurodevelopment of preterm infants and that the neurodevelopmental advantage of human milk may be related to its taurine content. Thus the new data provide further support for the view that taurine is a conditionally essential nutrient for the preterm infant. They also provide an additional example of apparent long term effects of short term early differences in nutrient intake.

The findings of Wharton *et al* also present a quandary. Randomised, controlled trials of taurine supplementation for both preterm and term infants should clearly be the next step, but would either trial now be ethical? Like so many other issues in neonatal nutrition and, indeed, all of clinical medicine, it is unlikely that the role of taurine in infant nutrition will ever be evaluated in a randomised controlled trial.

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