



Omega Bio-Pharma (U.S.A.) LLC

Feb. 3, 2004

Division Director,
Division of Dietary Supplements Programs,
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820),
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway,
College Park, MD 20740, U.S.A.

Attn: Dr. Susan Walker

Dear Dr. Walker,

RE: 75-DAYS PREMARKET NOTIFICATION

This letter is writing to supplement the outstanding information requested in the fax dated 2 Feb. 04 regarding the basis of "2-aminoethanethiol hydrochloride" as a dietary ingredient for the product names of AK-40, S-BI, and S-BR. This chemical has been clarified in the letter dated Jan. 6. 2004 for the product of BIR-26.

2-aminoethanethiol hydrochloride is also called cysteamine hydrochloride. Cysteamine exists naturally by decarboxylation of cysteine or enzymatic cleavage of co-enzyme A, which will ultimately be metabolized to taurine. As a result, the compound is considered as a dietary supplement since it is the metabolite of an amino acid.

Yours Sincerely,

For and on behalf of
Omega Bio-Pharma (U.S.A.) LLC

Gary Wong
Assistant Sales Manager

Encl.: A figure of metabolic pathway.

Metabolic Pathway of Cysteamine

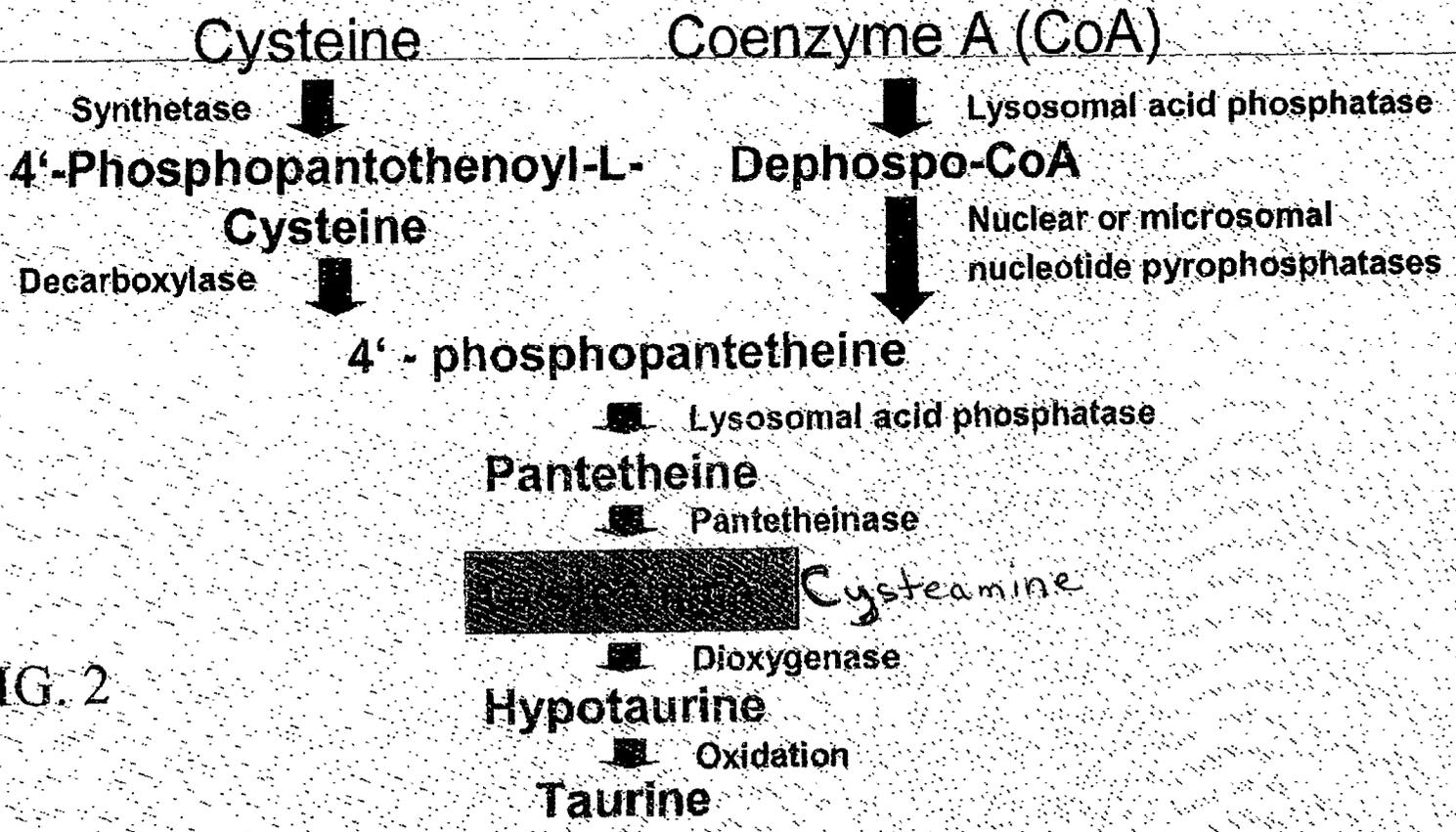


FIG. 2



FEB - 2 2004

Mr. Gary Wong Kwan Po
Assistant Sales Manager
Unit 714 7/F
Miramar Tower
1-23 Kimberly Road
Tsimishatsui, Kowloon
Hong Kong SAR

Dear Mr. Po:

This is to inform you that the notification dated November 18, 2003 that you submitted pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on November 20, 2003. Your notification concerns the substance "2-aminoethanethiol hydrochloride," also known as cysteamine hydrochloride (HCl) that you intend to market as a new dietary ingredient under the product name, "S-BI."

According to the notification, you intend to sell 300 milligram (mg) capsules containing 81 mg of cysteamine HCl (this provides 55 mg of cysteamine base per capsule). You describe the other ingredients in each capsule as Aspartic Acid (0.75 mg), Threonine (0.30 mg), Serine (3.00 mg), Glutamic Acid (0.70 mg), Glycine (22.00mg), Alanine (25.00mg), Valine (0.25 mg), Leucine (0.10 mg), Throsine (0.50 mg), Arginine (0.10 mg), and Lysine (0.15 mg). Your facsimile dated January 6, 2004 stated that the correct amount of starch and avicel in the product is 87 mg and 79.15 mg per capsule, respectively. Under the conditions of use stated in the labeling of your product you indicate that the suggested dosage is "3-4 capsules each, 2 times daily in the morning and at night." Under precautions you state "Keep out of reach of children. Store in cool, dry place, tightly closed. Protect from light. This product contains a dessicant for maximum potency and freshness."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be

adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

It is unclear on what basis you assert that "2-aminoethanethiol hydrochloride" that is the subject of your notification is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

FDA requests that you submit information explaining your basis for asserting that 2-aminoethanethiol hydrochloride falls under the definition of dietary ingredient in 21 U.S.C. 321(ff)(1).

In addition, your notification presents a novel issue for FDA to consider with respect to whether the product includes an article that has been approved as a new drug under 21 U.S.C. 355 (21 U.S.C.321(ff)(3)(B)(i)). FDA intends to complete its evaluation shortly and send you a response to your notification explaining FDA's decision about whether your products are dietary supplements within the meaning of 21 U.S.C. 321(ff).

This letter is to alert you within the 75-day notification period that FDA has concerns about whether your product can lawfully be marketed as a dietary supplement. Please note that failure to respond to a notification within the 75-day timeframe does not constitute a finding by the agency that the ingredient or a product that contains the ingredient is safe or is not adulterated under 21 U.S.C. 342. 21 C.F.R. 190.6(f).

If you have any questions or would like to arrange a meeting concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,



Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition



Omega Bio-Pharma (U.S.A.) LLC

Jan 6, 2003

Attention: Dr. Susan Walker

Cc: Vickey Lutwak

Division of Dietary Supplements Programs,
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820),
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway,
College Park, MD 20740, U.S.A.

Dear Ms. Walker,

RE: 75-DAYS PREMARKET NOTIFICATION

Referring to our previous applications for products: SB-L, AK-40, and SB-R, we are sorry to tell you that there were wrong figures in the amount of "other ingredients" i.e. starch and avicel.

For SB-L, the amount of the starch and avicel should be 87 mg per capsule and 79.15 mg per capsule respectively.

For AK-40, the amount of the starch and avicel should be 81 mg per capsule and 72.45 mg per capsule respectively.

For SB-R, the amount of the starch and avicel should be 88 mg per capsule and 78.95 mg per capsule respectively.

Yours Sincerely

For and on behalf of

Omega Bio-Pharma (U.S.A.) LLC

Gary Wong Kwan Po
Assistant Sales Manager

Encl.: One original and two copies of the 75-Days Premarket Notification for New Dietary Ingredient for each product.



Omega Bio-Pharma (U.S.A.) LLC

November 18, 2003

Division Director,
Division of Dietary Supplements Programs,
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820),
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway,
College Park, MD 20740, U.S.A.

RECEIVED
NOV 20 2003
BY: R.B. / FDA

Attn.: Ms. Susan Walker

Dear Ms. Walker,

RE: 75-DAYS PREMARKET NOTIFICATION

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, Omega Bio-Pharma (U.S.A.) LLC, located at Suite 606, 1220 N. Market Street, Wilmington, County of New Castle, Delaware, DE 19801, United States of America, submits this New Dietary Ingredient 75-Days Premarket Notification to the Food and Drug Administration ("FDA") for 2-Aminoethanethiol Hydrochloride.

We take this action with understanding that Omega Bio-Pharma (U.S.A.) LLC will not market this product for a period of at least 75 days after the FDA receipt of this notification. We believe that this New Dietary Ingredient Notification submission should provide the information that FDA requires. If there is any question concerning this submission, please feel free to contact me at pleung@omega-biopharma.com or by fax at (852) 2494-0112. Thank you very much.

Yours Sincerely

For and on behalf of

Omega Bio-Pharma (U.S.A.) LLC

Gary Wong Kwan Po
Assistant Sales Manager

For and on behalf of
WALCOM BIO-CHEMICALS (USA) LLC

.....
Authorised Signature(s)

Encl.: One original and two copies of the 75-Days Premarket Notification for New Dietary Ingredient.



Omega Bio-Pharma (U.S.A.) LLC

ORIGINAL

NEW DIETARY INGREDIENT

LB/FOA

75-DAYS PREMARKET NOTIFICATION

Attachment

(2-AMINOETHANETHIOL HYDROCHLORIDE)

Submitted by

OMEGA BIO-PHARMA (U.S.A.) LLC

NAME & ADDRESS OF DISTRIBUTOR

Registered Office:

Omega Bio-Pharma (U.S.A.) LLC
Suite 606, 1220 N. Market Street,
Wilmington, County of New Castle,
Delaware, DE 19801
United States of America

Correspondence Address:

Omega-Pharma (Hong Kong) Limited
Unit 714, 7/F., Miramar Tower,
1-23 Kimberley Road, Tsimshatsui,
Kowloon, Hong Kong SAR
Tel: (852) 2494-0133
Fax: (852) 2494-0112
Email: enquiry@omega-biopharma.com

NAME OF THE NEW DIETARY INGREDIENT

Name: **2-Aminoethanethiol Hydrochloride**

Other Chemical Names: Cysteamine Hydrochloride,
 β -Mercaptoethylamine hydrochloride,
2-Mercaptoethylamine hydrochloride,
Thioethanolamine hydrochloride,
Decarboxycysteine hydrochloride

CAS Number: 156-57-0

Molecular Formula: C₂H₇N.S.Cl-H

Molecular Weight: 113.62

DESCRIPTION OF THE NEW DIETARY SUPPLEMENT

I. Level of the new dietary ingredient in the product:

Product Name: S-BI

SUPPLEMENT FACTS

Serving Size 1 capsule
Each serving contains total 300 mg

Major Ingredients

| | |
|----------------------------------|---------|
| 2-Aminoethanethiol Hydrochloride | 81.00mg |
| Aspartic Acid | 0.75mg |
| Threonine | 0.30mg |
| Serine | 3.00mg |
| Glutamic Acid | 0.70mg |
| Glycine | 22.00mg |
| Alanine | 25.00mg |
| Valine | 0.25mg |
| Leucine | 0.10mg |
| Throsine | 0.50mg |
| Arginine | 0.10mg |
| Lysine | 0.15mg |

Other Ingredients

| | |
|--------|---------|
| Starch | 60.00mg |
| Avicel | 54.00mg |

II. Conditions of use of the product stated in the labeling:

Suggested Dosage

3-4 capsules each, 2 times daily in the morning and at night

Precautions

Keep out of reach of children. Store in cool, dry place, tightly closed. Protect from light.

This product contains a dessicant for maximum potency and freshness.

III. Safety Evidence of the Dietary Ingredient

Pharmacodynamic and Pharmacokinetic Study

2-Aminoethanethiol Hydrochloride (Cysteamine Hydrochloride / Cysteamine) is the endogenous and physiological/natural constituent of mammalian tissues, however, as a free form, in very low concentration⁽¹⁸⁾.

Cysteamine is present naturally in human and animal body^(11, 15) as :

- a protein-bound form (cysteamine as a moiety of CoA and respectively, acyl-carrier-protein in the central protein-component of fatty acid-synthase-complex);
- a free reduced form;
- and as a free oxidized forms (total free form), i.e. cystamine and mixed disulfides with low molecular weight thiols such as cysteine, homocysteine or glutathione.

Above mentioned forms in mice, at physiological levels, have follow distribution (see Table 1)⁽¹⁵⁾.

Table 1. Total cysteamine contents and percentages of the different forms of cysteamine in mouse tissues (at phasiological levels)⁽¹⁵⁾.

| Tissue | Total cysteamine (nmol*/g) | Cysteamine (%)* | | |
|-----------|-------------------------------|-----------------|---------------|---------------|
| | | Reduced | Free oxidized | Protein-bound |
| Eye | 46.3 | 0 | 58.5 | 41.5 |
| Brain | 54.4 | 3.9 | 33.8 | 62.3 |
| Heart | 66.6 | 3.8 | 67.0 | 29.3 |
| Lung | 79.6 | 2.8 | 45.9 | 51.4 |
| Liver | 53.8 | 18.0 | 68.0 | 13.9 |
| Spleen | 10.7 | 17.8 | 43.0 | 39.3 |
| Pancreas | 17.1 | 40.9 | 32.2 | 26.9 |
| Kidney | 106.7 | 65.9 | 27.8 | 6.3 |
| Stomach | 18.5 | 18.9 | 50.8 | 30.3 |
| Intestine | 33.3 | 21.0 | 41.1 | 37.8 |
| Testis | 16.0 | 28.8 | 50.6 | 20.6 |
| Muscle | 9.6 | 16.7 | 46.9 | 36.5 |

* The cumulative values of the reduced cysteamine, free oxidized cysteamine (cystamine and mixed disulfides with low molecular weight thiols) and protein-bound cysteamine were taken as 100% (total cysteamine).

** 1 nmol cysteamine-free base corresponds to 0.0771 µg cysteamine free-base.

Data in Tables 1 show evident that free cysteamine form at the natural physiological levels is distributed in mouse tissue widely, except the eye. At the same time, the kidney contain highest concentrations of free cysteamine. Moreover, kidney, heart, liver and lung contained elevated levels of protein-bound cysteamine.

On account of difficulties with directly obtainment of exact cysteamine-concentration in biological tissues/food products (cysteamine rapidly oxidized to cystamine or hypotaurine, as intermediate), the calculation of its amount is based on the equal rate of the cysteamine and pantothenic acid molecules, as far as they substances are products of coenzyme A (CoA) degradation. Moreover, from investigations of CoA-metabolic pathway (which is a main source of cysteamine releasing), the concentration of pantothenic acid (as quite stable substance, more than oxidized cysteamine) is the best assayed.

The concentrations of pantothenic acid in foodstuff are well known. Therefore, a natural concentration of cysteamine, estimated from the value of pantothenic acid contents in food products (1 molecule of cysteamine free-base, i.e. 77 g, corresponds to 1 molecule pantothenic acid, i.e. 220 g or: 1 µg pantothenic acid corresponds to 0.35 µg cysteamine free-base), are presented below in Table 2.

Table 2. Estimated values of cysteamine from natural concentration of pantotheic acid^(4, 15, 26).

| Products | Pantothenic acid* | Cysteamine (base) |
|-------------------|---------------------|-------------------|
| | [µg / 100g product] | |
| Cow's milk | 350 | 124 |
| Human milk (µg/l) | 6700 | 2345 |
| Yogurt | 350 | 124 |
| Eggs | 1600 | 560 |
| Yolk | 3720 | 1302 |
| Butter | 47 | 16 |
| Veal | 850 | 298 |
| Veal liver | 7900 | 2765 |
| Veal kidney | 4000 | 1400 |
| Veal lungs | 1000 | 350 |
| Beef (meat) | 1000 | 350 |
| Oxkidney | 3800 | 1330 |
| Oxliver | 7300 | 2555 |
| Pork | 700 | 245 |
| Porcine liver | 6800 | 2380 |
| Porcine heart | 2500 | 875 |
| Porcine kidney | 3100 | 1085 |
| Lamb's liver | 8250 | 2887 |
| Lamb's kidney | 4520 | 1582 |
| Hen (meat) | 840 | 294 |
| Hen's liver | 7160 | 2506 |
| Hen's heart | 2560 | 896 |

| | | |
|--------------------|------|-------|
| Turkey hen (meat) | 1050 | 367 |
| Herring (East See) | 9300 | 3260 |
| Fish trout | 1720 | 602 |
| Heilibut | 305 | 106 |
| Bread roll | 960 | 336 |
| Sliced white bread | 230 | 805 |
| Flour wheaten | 1200 | 420 |
| Rice | 1700 | 595 |
| Cheese camembert | 900 | 315 |
| Honey | 940 | 327 |
| Chocolate | 900 | 315 |
| Potatoes | 400 | 140 |
| Softhead lettuce | 180 | 63 |
| Cauliflower | 1010 | 353.5 |
| Red cabbage | 320 | 112 |
| White cabbage | 260 | 91 |
| Tomato | 310 | 109 |
| Spinach | 250 | 88 |
| Bean | 870 | 305 |
| Pea | 720 | 252 |
| Soya bean | 1860 | 651 |
| Asparagus | 620 | 217 |
| Peanut | 2700 | 945 |
| Champignon | 2100 | 735 |
| Black currant | 400 | 140 |
| Banana | 230 | 85 |
| Apricot | 290 | 102 |
| Orange | 240 | 84 |
| Apple | 100 | 35 |
| Beer yeasts | 7210 | 2524 |

1 µg pantothenic acid corresponds to 0.35 µg of cysteamine-free base.

Toxicity

The toxic effect of cysteamine depends on, obviously, a dose and kind of application, kind of treated animal as well as conditions of action. The following table (Table 3) review the toxicity of single and repeated doses of cysteamine which are related to the route of administration as well as species target of animal or human.

Table 3: Acute & Chronic Toxicity of Cysteamine

| Species | Route of administrtion | mmol/kg b.w. | References |
|---------|------------------------|------------------------------|--|
| Mouse | per oral (po) | 8.10 LD ₅₀ | Srivastava & Field, 1975 ⁽²⁸⁾ |
| Mouse | sc | 3.20+0.15 LD ₅₀ | Koch & Schwarze, 1957 ⁽¹⁹⁾ |
| Mouse | intraperitoneal (ip) | 3.24 LD ₅₀ | Srivastava & Field, 1975 ⁽²⁸⁾ |
| Mouse | ip | 2.20 LD ₅₀ | Klayman et al., 1969 ⁽¹⁸⁾ |
| Rat | ip | 2.04 LD ₅₀ | Beccari et al., 1955 ⁽¹⁾ |
| Rabbit | intravenous (iv) | 1.32 LD ₅₀ | Beccari et al., 1955 ⁽¹⁾ |
| Human | po | 0.39-1.17/d, 30 month noe | Yudkoff et al., 1981 ⁽³⁰⁾ |
| Human | iv | 41.48 mmol/person | |

in 16 h noa

Harris, 1982⁽⁶⁾

** noa - no available; 1 mmol of cysteamine-free base corresponds to 77 mg of cysteamine-free base.*

Mutagenicity

The cysteamine molecule fulfill with its sulph-hydryl- and aminogroup in the distance of two atoms of carbon all suppositions in structure of an antimutagenic agent⁽²⁶⁾. In microbiological test systems it lowers the spontan rate of chromosome aberrations⁽²⁾ and inhibit in dose depending kind the chromosome damage of mutagens like maleic hydrazide, 8-hydroxyquinolinesulphate, triaziqune, triethylthiophosphoramide (Thio-TEPA) etc. in human cell c ultures⁽⁷⁾. The antimutagenic p roperties o f c ysteamine r epair⁽⁸⁾. A r ole may also play the nucleophilic properties of cysteamine.

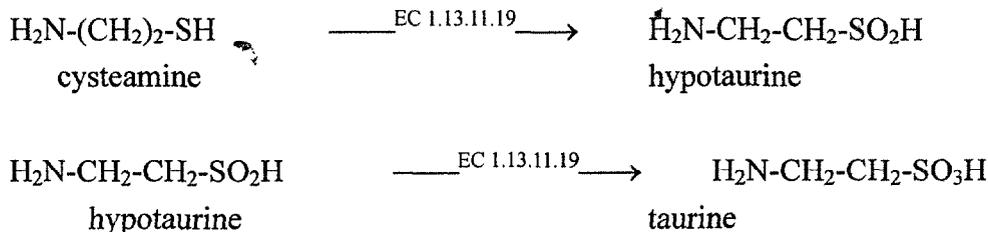
Carcinogenicity

Cysteamine hydrochloride inhibits the induction of mammary carcinoma in rats by 7, 12-dimethylbenz(a)anthracene^(20, 32) and also the development of transformed foci in cultivated mice-fibroblasts⁽²⁰⁾. A comparable inhibition activity is also known of other thiocompounds⁽²⁸⁾. Cysteamine seems to be another example of the “amazing parallels between mutagenicity and carcinogenicity”⁽⁸⁾ of chemical substances. The main cause for the inhibition of chemical carcinogenicity can be the nucleophilia of the cysteamine molecule.

Metabolism

Metabolism of cysteamine is involved in the alternative pathway of taurine biosynthesis in mammals organs, especially heart (a major source of cardiac taurine), and also in human liver as well as in their kidney⁽¹²⁾.

At first enzyme dioxygenase (EC 1.13.11.19. IUBMB, 1992) catalyzes the irreversible oxidation of natural cysteamine levels (and also administered that one, but at a dose less than 100 mg/kg) to hypotaurine (as an intermediate) and then oxidizes its further to taurine. Taurine (2-aminoethanesulfonic acid) is a physiologically important substance in many organs (especially in heart, and in the central nervous system) as well as it plays some role by conjugation of bile acid (25%) in man and inhibits digitalis-induced arrhythmias^(12, 23, 25, 29, 31). Production of taurine from cysteamine (at physiological levels) is at very low concentration, i.e. less than 3 nmoles/g fresh tissue of man^(3, 12). Finally, taurine is excreted for the rest renally⁽³¹⁾:



For human, treated by cysteamine at doses of 5 or 10 mg/kg, the **half-times ($T_{1/2}$) for loss of cysteamine from the plasma**, based upon the 30- and 90-min values, were 18 min for the 5 mg/kg dose and 20 min for the 10 mg/kg dose. Five to seven hours after a cysteamine dose of 5 mg/kg, plasma cysteamine was undetectable, i.e. $<1.3 \mu\text{M}$ (see Fig. 2).

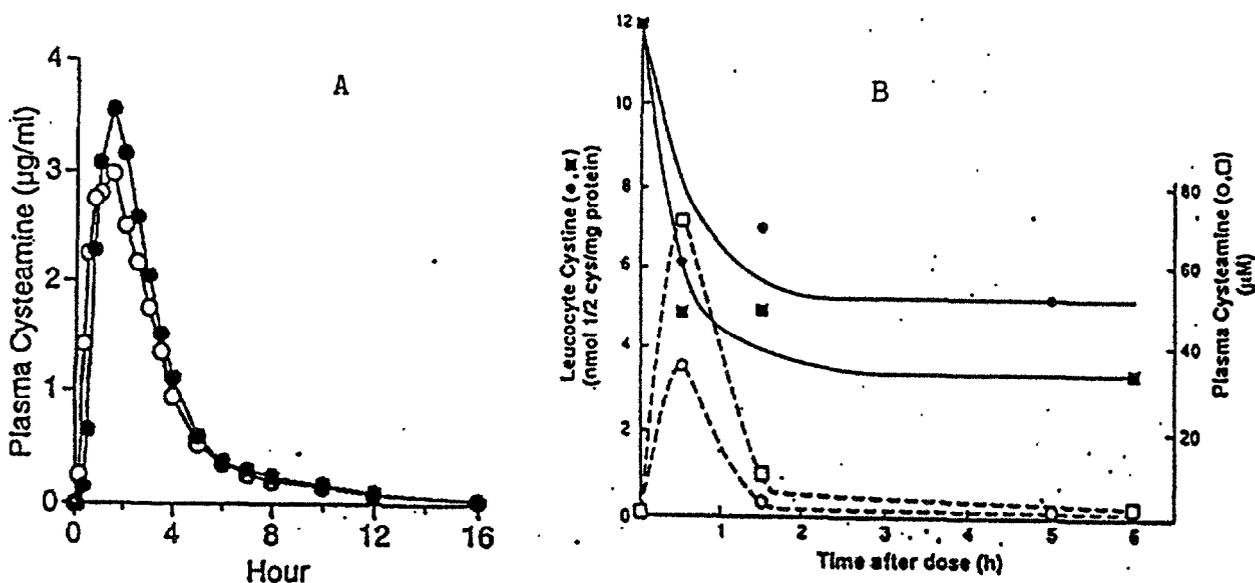


Fig. 2. A - Plasma cysteamine concentration following either cysteamine hydrochloride solution (μ) or cysteamine bitartrate capsules (λ) in 24 normal control subjects ⁽²⁷⁾. B - Lukocyte cystine levels and plasma cysteamine concentrations after i.v. doses of cysteamine into patients with nephropathic cystinosis. A single dose of 5 mg/kg (75 mg of cysteamine-free base: μ , λ) or 10 mg/kg (150 mg of cysteamine-free base: \square , ν) was injected into the patient's central line in a volume of 50 ml of normal saline over 20 min. and blood was sampled after various times ⁽⁵⁾.

The relatively short half-life ($T_{1/2}$) of cysteamine **in human plasma**, approximately 20 min., what was reported by Gahl and co-workers ⁽⁵⁾, reflects its conversion to excretable sulfur-containing compounds. Jonas and Schneider ⁽¹⁴⁾ have reported only 0.3-1.7% of an oral dosage of 6.6-15.8 mmol/day (i.e. 508-1217 mg/day) excreted intact in the urine, indicating that other metabolites must be involved, e.g. dimethylsulfide.

Recently, Gahl and co-workers proposed an additional pathway in cysteamine catabolism ⁽⁵⁾.

| Subject | Age | Sex* | Total cysteamine* (nmol/mg creatinine) |
|---------|-----|------|---|
| 1 | 7 | M | 4.09 ± 0.01 |
| 2 | 23 | M | 1.53 ± 0.11 |
| 3 | 23 | M | 2.53 ± 0.02 |
| 4 | 24 | M | 1.00 ± 0.06 |
| 5 | 38 | M | 1.51 ± 0.01 |
| 6 | 5 | F | 2.88 ± 0.02 |
| 7 | 20 | F | 2.68 ± 0.02 |
| 8 | 21 | F | 0.59 ± 0.03 |
| 9 | 22 | F | 0.77 ± 0.03 |
| 10 | 38 | F | 1.93 ± 0.01 |

* M: male; F: female; ** Mean ± S.D. (n=4). 1 nmol CSH corresponds to 77.13 µg cysteamine free-base/ml.

Conclusion

Based upon the above references, we conclude that the new dietary ingredient - 2-Aminoethanethiol Hydrochloride, is considered as a natural and safety compound to use at the recommended maximum oral daily dosage.

References

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