

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

JAN 29 2004
OB/FDA

NEW DIETARY INGREDIENT

75-DAYS PREMARKET NOTIFICATION

Attachment

(2-AMINOETHANETHIOL HYDROCHLORIDE)

Submitted by

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



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

January 20, 2004

Attention: 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

JAN 29 2004
Ω-BI/FDA

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

1. 2-Aminoethanethiol Hydrochloride of product S-BI II

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 gary@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

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

87113

NAME & ADDRESS OF DISTRIBUTOR

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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 II

SUPPLEMENT FACTS

Serving Size 1 capsule
Each serving contains total 300 mg

Major Ingredients

Alanine	25.00mg
Glycine	22.00mg
Serine	3.00mg
Arginine	0.10mg
Throsine	0.50mg
Threonine	0.30mg
2-Aminoethanethiol Hydrochloride	81.00mg

Other Ingredients

Starch	88.50mg
Avicel	79.60mg

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 desiccant 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 physiological 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-hydril- 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, triaziquone, triethylthiophosphoramidate (Thio-TEPA) etc. in human cell cultures⁽⁷⁾. The antimutagenic properties of cysteamine repair⁽⁸⁾. A role may also play the nucleophilic properties of cysteamine.

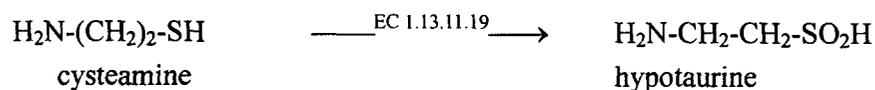
Carcinogenicity

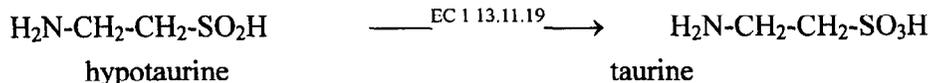
Cysteamine hydrochloride inhibits the induction of mammary carcinoma in rats by 7, 12-dimethylbenz(a)anthracene^(20, 32) and also the development of transformed foci in cultivated mice-fibroblasts⁽²⁰⁾. A comparable inhibition activity is also known of other thiocompounds⁽²⁸⁾. Cysteamine seems to be another 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).

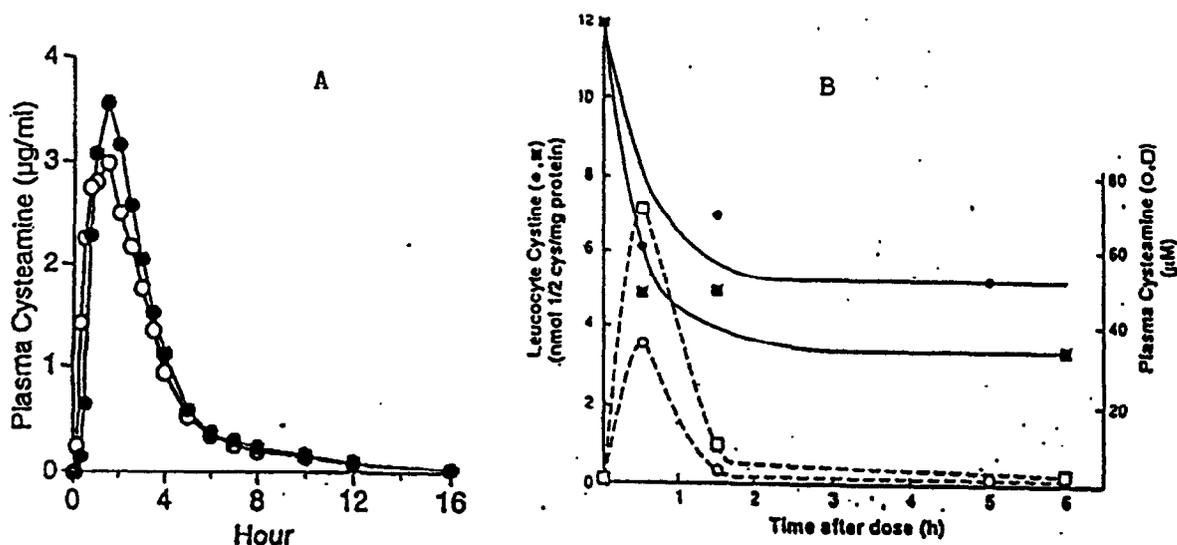


Fig. 2. A - Plasma cysteamine concentration following either cysteamine hydrochloride solution (μ) or cysteamine bitartrate capsules (λ) in 24 normal control subjects ⁽²⁷⁾. B - Lukocyte cystine levels and plasma cysteamine concentrations after i.v. doses of cysteamine into patients with nephropathic 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: 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⁾. The reason of that was identifying the presence of dimethylsulfide in breath and urine in treated patients with nephropathic cystinosis. Dimethylsulfide has not previously been identified as a metabolite of natural cysteamine. Authors suggested that cysteamine is at first

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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