



Memorandum

MAK 11 2004

Date: _____
From: Interdisciplinary Scientist/Pharmacist , Division of Dietary Supplement Programs
, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

Subject of the Notification: 2-Aminoethanethol hydrochloride (cysteamine HCL)
(AK-40)

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

Date Received by FDA: 11/20/03

90-Day Date: 2/18/04

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Gloria Chang

955-0316

RPT219



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 (HES-820),
Center for Food Safety and Applied Nutrition,
Food and Drug Administration,
5100 Paint Branch Parkway,
College Park, MD 20740, U.S.A.

~~FEB 20 2004~~
~~OB/EDA~~
~~FEB 07 2004~~

Attn.: Dr. Susan Walker

~~FEB 06 2004~~
FEB -4 2004
Reilly

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 tarine. 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.

87113

Cysteamine – Constituent of Co-enzyme A

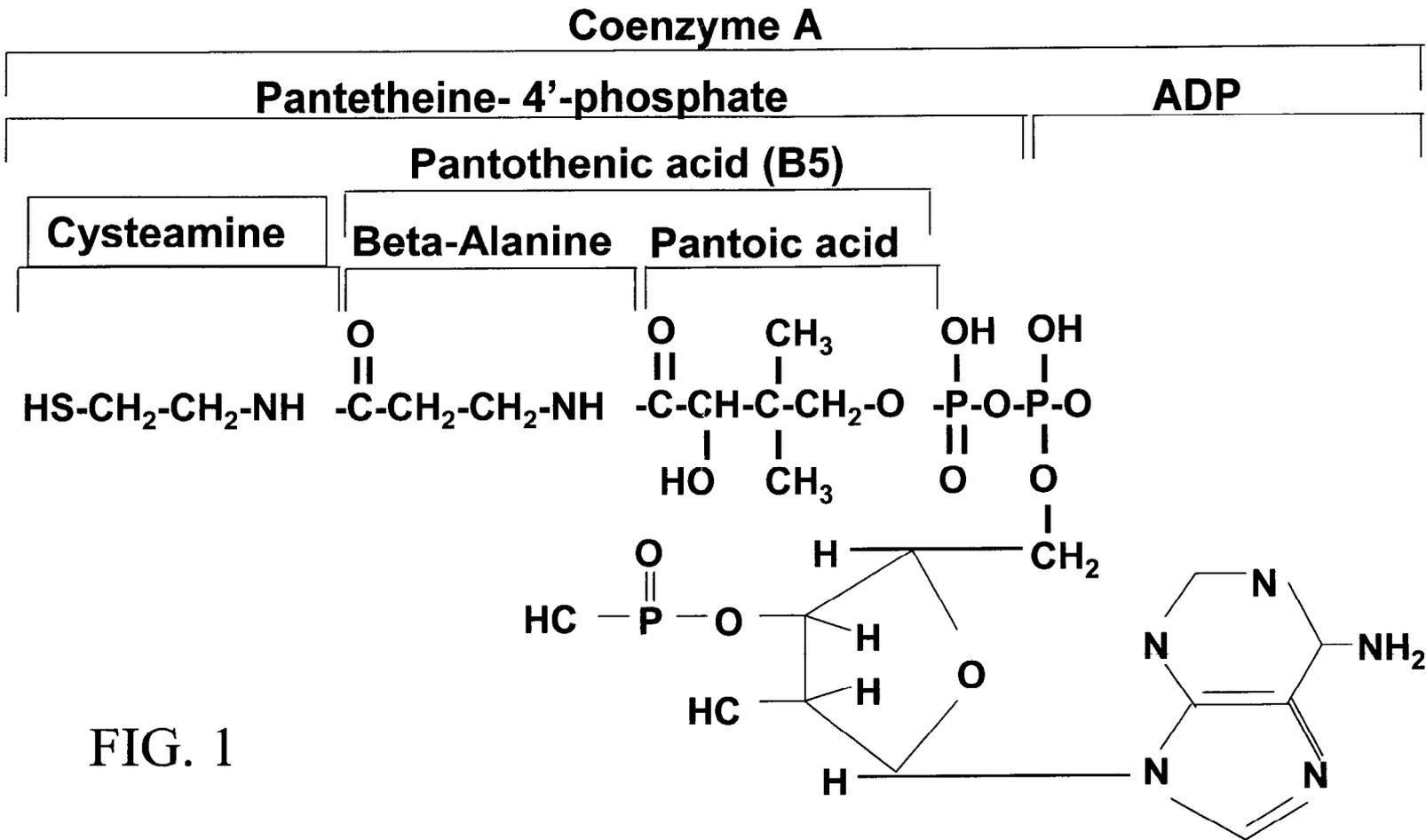


FIG. 1

Metabolic Pathway of Cysteamine

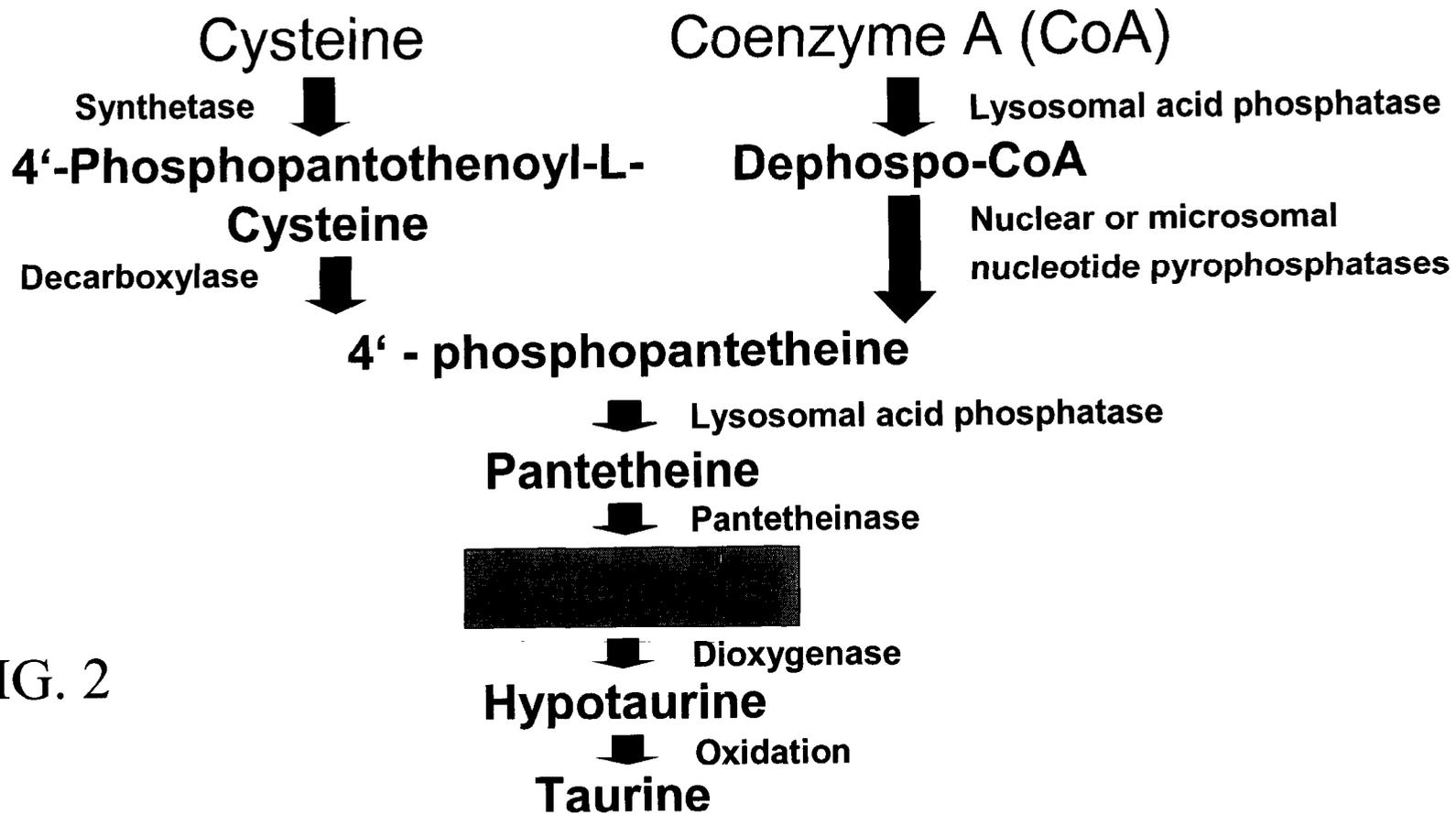


FIG. 2



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, "AK-40."

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 L-aspartic acid (0.75 mg), L-serine (3.00 mg), L-glutamic acid (0.70 mg), L-glycine (22.00 mg), L-alanine (25.00 mg), L-tyrosine (0.50 mg), and L-arginine (0.10 mg) and daidzin (13.5 mg). Your facsimile dated January 6, 2004 stated that the correct amount of starch and avicel in the product is 81 mg and 72.45 mg per capsule, respectively. Under the conditions of use stated in the labeling of your product you indicate that the suggested dosage is "4-8 capsules before 1-2 hours before drink." 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 (cysteamine) 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 with stamp date on 20 Nov 2003 for products : SB-I, 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-I, 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 Kwai 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 RBJ/FOA

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

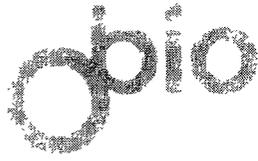
Omega Bio-Pharma (U.S.A.) LLC

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

OB/FOA

NEW DIETARY INGREDIENT

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: AK-40

SUPPLEMENT FACTS

Serving Size 1 capsule
Each serving contains total 300 mg

Major Ingredients

2-Aminoethanethiol Hydrochloride	81.00mg
L-aspartic Acid	0.75mg
L-serine	3.00mg
L-glutamic Acid	0.70mg
L-glycine	22.00mg
L-alanine	25.00mg
L-tyrosine	0.50mg
L-arginine	0.10mg
Daidzin	13.5mg

Other Ingredients

Starch	60.00mg
Avicel	54.00mg

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

Suggested Dosage

4-8 capsules before 1-2 hours before drink

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 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	1100	385
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, 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.

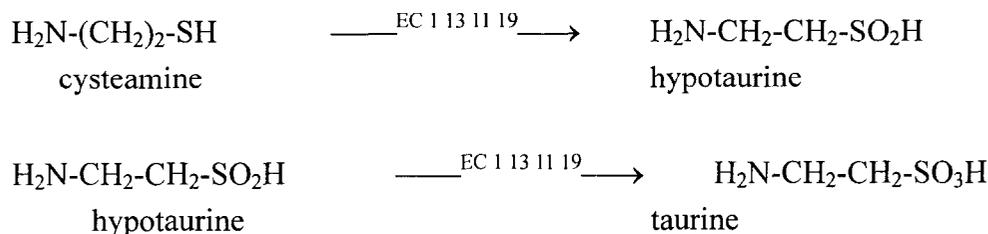
Carcinogenicity

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 dioxxygenase (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).

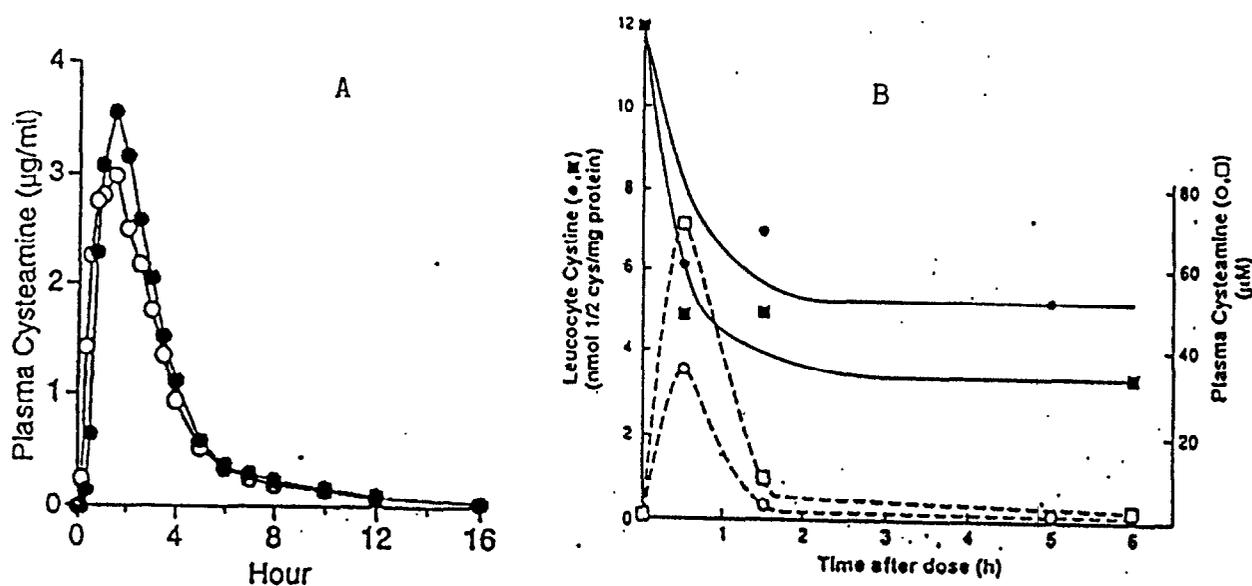
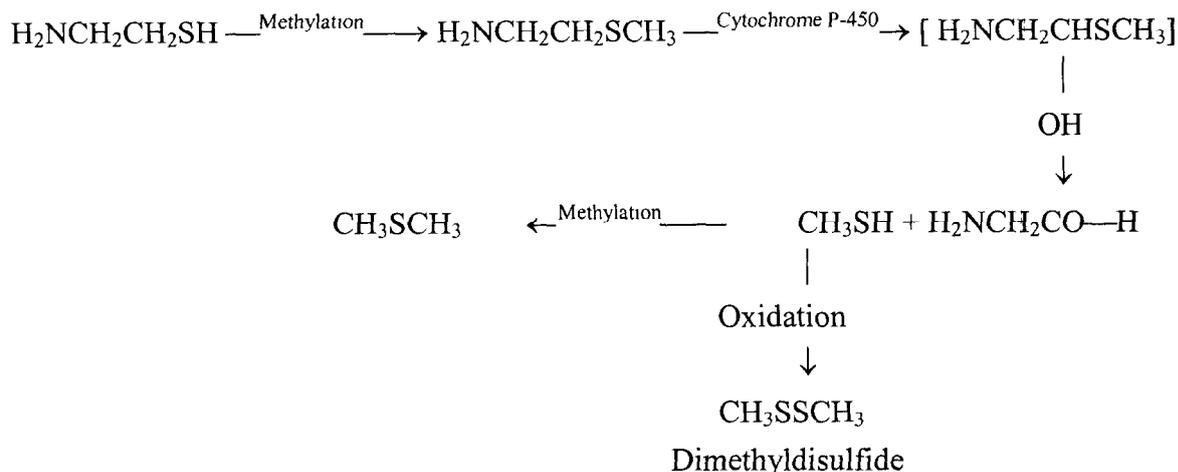


Fig. 2. A - Plasma cysteamine concentration following either cysteamine hydrochloride solution (μ) or cysteamine bitartrate capsules (λ) in 24 normal control subjects ⁽²⁷⁾. B - Leucocyte cystine levels and plasma cysteamine concentrations after i.v. doses of cysteamine into patients with nephropathic 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 , v) 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 methylated to the thioether, followed by a cytochrome P-450-mediated S-dealkylation of the thioether to methanethiol and a second methylation to dimethylsulfide, i.e.:



The breakdown of cysteamine to dimethylsulfide and dimethyldisulfide must be of mammalian origin ⁽⁵⁾. That methanethiol as an intermediate is supported by the presence of small amounts of dimethyldisulfide (the oxidation product of methanethiol) in the patient's breath ⁽⁵⁾. For further details, see p. 2.4., below.

Generally, *in vivo* facile oxidation of cysteamine results in a variety of disulphide forms, including cystamine and mixed disulphides (such dimethylsulfide) with low molecular weight thiols (such as cysteine, homocysteine and glutathione) and proteins ⁽¹⁶⁾.

Excretion

Although physiological cysteamine concentrations have been reported in several tissues ^(24, 13, 6), cysteamine levels in biological fluids are published weakly. Cysteamine (in majority, not metabolized to taurine) is eliminated from body renally and its biological half-life ($T_{1/2}$) period (metabolisation and output) in man, hamster and rats is in the range of 0.5 to 3 hours. There are not known informations about cattle and pig and also about other external excretion way, such through milk gland.

In Table 6 are shown the urinary excretion and plasma concentrations of total cysteamine (at physiological level) in several healthy volunteers ⁽¹⁷⁾.

Table 6. Urinary excretion of total cysteamine (at physiological level) in normal subjects.

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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