

# Collier Shannon Scott

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January 26, 2005

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VL/For

**VIA HAND DELIVERY**

**Confidential**

Ms. Victoria Lutwak  
Food and Drug Administration  
Center for Food Safety and  
Applied Nutrition  
5100 Paint Branch Parkway  
College Park, MD 20740-3835


**Re: NDI Notification for Spermidine Trihydrochloride**

Dear Ms. Lutwak:

Enclosed you will find the original and two copies of a New Dietary Ingredient Notification for the ingredient Spermidine Trihydrochloride. I am filing this on behalf of our client, Giuliani Sp.A. This Notification is being filed pursuant to the Dietary Supplement Health and Education Act, and 21 C.F.R. §190.6. Pursuant to that regulation, you will find attached to this NDI Notification, copies of all of the articles and reports cited therein.

If you should have any questions about this submission, please contact me at 202-342-8879, or at [iwasserman@colliershannon.com](mailto:iwasserman@colliershannon.com). Thank you in advance.

Sincerely,



Ivan J. Wasserman

Enclosures

cc: Dr. Sergio Baroni  
Farah K. Ahmed, Esq.

#90709

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Giuliani S.p.A. – Via Palagi, 2 – 20129 Milano – Telefono 02-20541 – Telefax 02-2054209

Milan, January 19<sup>th</sup>, 2005

Division of Standards and Labeling Regulations  
Office of Nutritional Products, Labeling and Dietary Supplements  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

**RE: NOTIFICATION OF NEW DIETARY INGREDIENT**

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 USC § 350b(a)(2), and consistent with the final regulations published by the FDA in the Federal Register of September 23, 1997 (62 Fed. Reg. 49886-49892), 21 CFR § 190.6, "Requirements for Premarket Notification", Giuliani SpA hereby submits the following information concerning a new dietary ingredient that Giuliani intends to begin marketing in dietary supplements.

Pursuant to the applicable provisions of DSHEA, Giuliani SpA will not introduce the ingredient or deliver it for introduction into interstate commerce until at least 75 days after the date FDA receives this notification.

**1. NAME AND ADDRESS OF DISTRIBUTOR**

The name and complete address of the distributor of the dietary supplement that contains the new dietary ingredient:

Giuliani S.p.A.  
Via P. Palagi 2  
I-20129 Milan  
ITALY

**2. NAME OF THE NEW DIETARY INGREDIENT**

Spermidine trihydrochloride.

**Chemical name**

N-(3-aminopropyl)-1,4-tetramethylenediamine trihydrochloride  
N-( $\gamma$ -aminopropyl)tetramethylenediamine trihydrochloride

**Chemical structure**



**Molecular formula**

$C_7H_{19}N_3 \cdot 3HCl$

**Molecular weight**

254.63

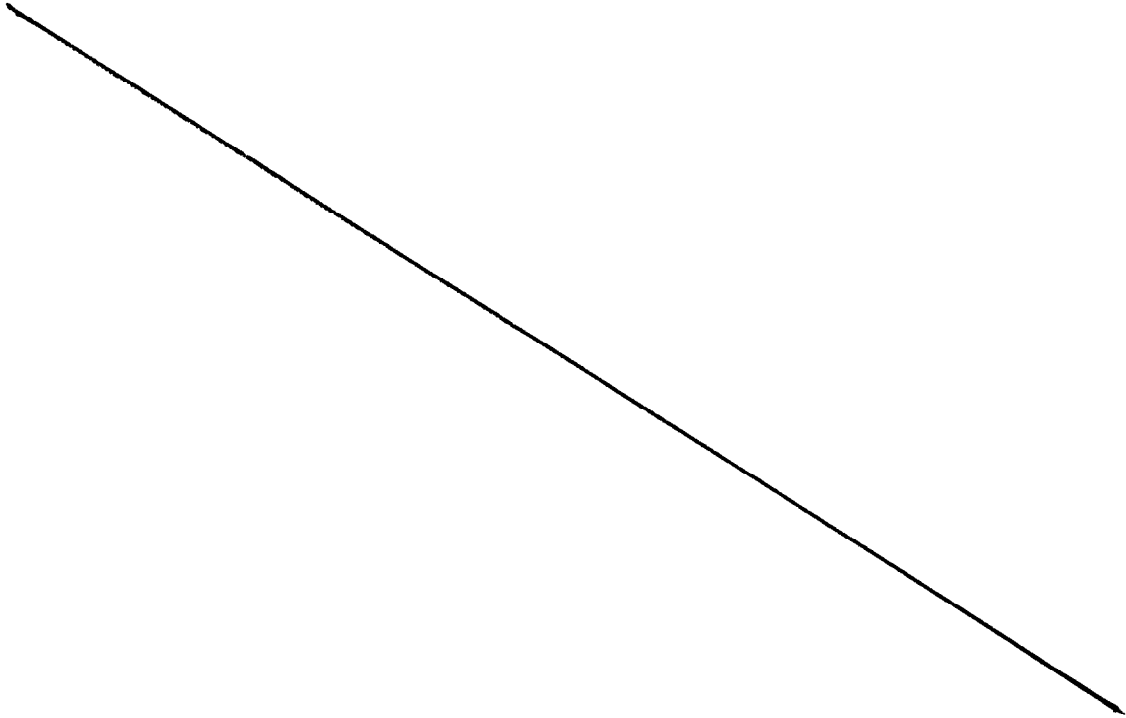
(free base: m.w. 145.25)

**CAS Registry number**

[334-50-9]

(Free base: [124-20-9])

## Purity



### **3. DESCRIPTION OF THE DIETARY SUPPLEMENTS THAT CONTAIN THE NEW DIETARY INGREDIENT**

Spermidine trihydrochloride will be a dietary ingredient in products that meet the definition of “dietary supplement” in section 201(ff) of the Federal Food, Drug, and Cosmetic Act. Spermidine trihydrochloride will be included in dietary supplements to supplement the diet by increasing the total dietary intake of the substance.

#### Level of the new dietary ingredient in the dietary supplement:

The dietary supplements will contain 0.25 – 0.50 mg of Spermidine trihydrochloride per tablet (corresponding to 0.143 mg/tablet and 0.285 mg/tablet of spermidine free base respectively).

#### Conditions of use:

Consumption of one tablet per day will be suggested, resulting in a range of consumption of 0.25 – 0.50 mg/day of Spermidine trihydrochloride, corresponding to 0.143 - 0.285 mg/day of Spermidine free base.

Tablets should be taken, preferably, in the morning with breakfast.

The directions will state that the product should not be used by children.



#### 4. BASIS FOR THE SAFETY OF SPERMIDINE TRIHYDROCHLORIDE

The base of the new dietary ingredient, spermidine, is an ubiquitous normal constituent of all prokaryotic and eukaryotic cells.

It owes its name to the presence in human sperm, from which it was first isolated (actually it is present in all body fluids, such as blood, saliva, tears, milk).

Spermidine endogenous biosynthesis is complex and may be summarized as follows: the starting compound of the biosynthetic pathway is the essential amino acid arginine. Arginine is firstly transformed in another amino acid, ornithine, and then is converted by ornithine decarboxylase (ODC) in putrescine (1,4-tetramethylenediamine). Putrescine, through specific amino-propylic radical donor enzymes, is transformed in the N-monoaminopropyl derivative (spermidine) and in the N,N'-diaminopropyl derivative (spermine), as illustrated below.

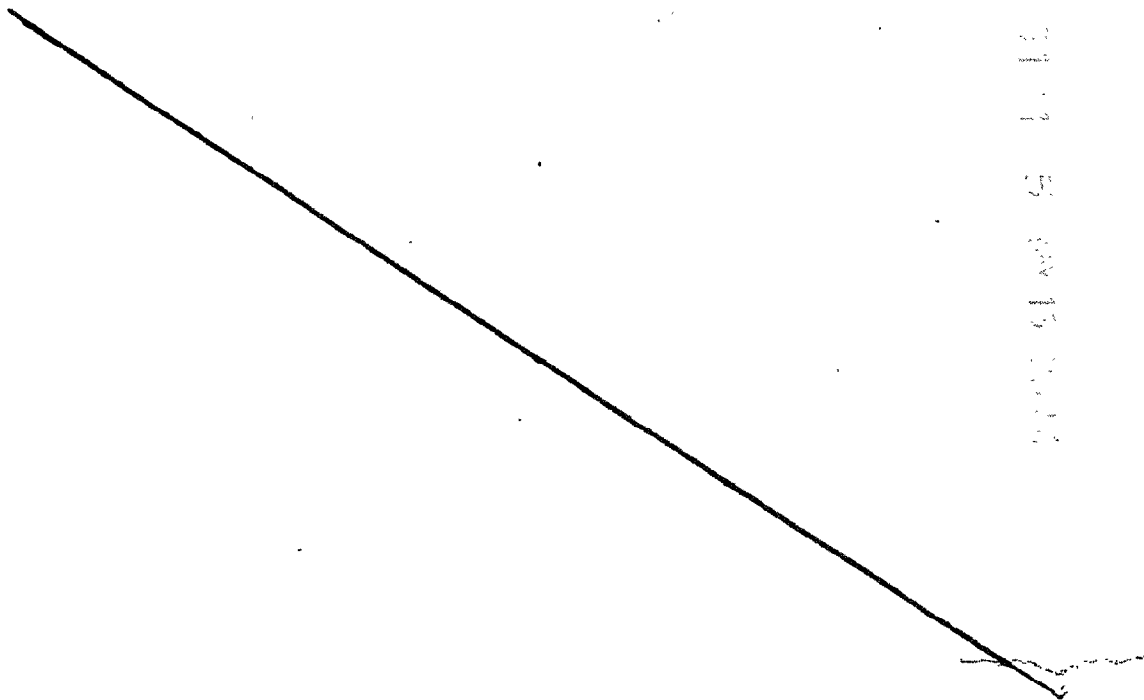


Figure 1

The overall safety of spermidine trihydrochloride is supported by the presence of spermidine in many foods either of animal origin (meat, fish, eggs, milk, cheese) or of vegetable origin (fruit and green vegetables).

Spermidine is present in milk, particularly human milk (an average of 600 µg in the milk of 24h) where it plays an important role for the newborn.

The presence of Spermidine was searched for in many common food products. The following table shows some data taken from literature. These data were converted, for direct comparison, in milligrams of spermidine free base per 100 g/mL of food product.

### Presence of spermidine in food

**Table 1**

Food type	Spermidine content		Ref.
	nmol/g or mL	mg/100 g or mL	
<b>Beverages</b>			
Beer	< 5	< 0.1	[1]
Coffee: Granules	18-24	0.3 - 0.3	[2]
Green Tea: Leaves	851	12.36	[1]
Tea: Leaves	252-274	3.7 - 4.0	[2]
Infusion	1-2	0.0 - 0.0	[2]
<b>Cereals</b>			
Corn	240	3.49	[1]
Jam tart	27-31	0.4 - 0.5	[2]
Mixed breakfast cereals (ten varieties)	166-168	2.4 - 2.4	[2]
Polished	27.0	0.39	[1]
Soy (dried beans)	1430	20.8	[1]
Sponge pudding	17-23	0.2 - 0.3	[2]
Wheat flour	66	0.96	[1]
<b>Egg</b>			
Boiled	0-1	0.01	[2]
<b>Fish</b>			
Fish in cheese sauce	20-24	0.3 - 0.3	[2]
Tuna fish	30	0.00	[1]
<b>Fruit products</b>			
Apple	7	0.00	[1]
Mandarin orange, raw	18-20	0.3 - 0.3	[2]
Peach, canned	15-19	0.2 - 0.3	[2]
Pears, canned	21-25	0.3 - 0.4	[2]
Raisins	6-11	0.1 - 0.2	[2]
<b>Meat</b>			
Beef, lean	18.00	0.26	[1]
Chicken	20	0.3	[1]
Irish stew (lamb, cooked)	55-62	0.8 - 0.9	[2]
Pork, lean	32	0.5	[1]
Sweet and sour pork (pork, cooked)	45-51	0.7 - 0.7	[2]
<b>Cheese</b>			
Blue cheese	20	0.3	[1]
<b>Milk</b>			
Cow	3.24	0.05	[3] - avg

**Table 1**

Food type	Spermidine content		Ref.
	nmol/g or mL	mg/100 g or mL	
Human	1.97	0.03	[3] - avg
Mushroom			
Enokidaka	600	8.71	[1]
Honshimeji	480	6.97	[1]
Shitake	890	12.93	[1]
Nuts			
Cashew nuts	255-266	3.7 - 3.9	[2]
Sugar and preserves			
Jam (four varieties)	12-18	0.2 - 0.3	[2]
Sugar (three varieties)	1-2	0.0 - 0.0	[2]
Vegetable products			
Carrots	55	0.8	
Chips	164-178	2.4 - 2.6	[2]
Lentil soup	148-155	2.1 - 2.3	[2]
Potato crisps (three varieties)	243-275	3.5 - 4.0	[2]
Potatoes	93	1.4	[1]
Spinach	120	1.7	[1]
Tomatoes	12	0.2	[1]

[1] Okamoto A, Sugi E et al. Polyamine content of ordinary foodstuff and various fermented foods, *Biosc Biotech Biochem* 1997; 61 (9): 1582-4

[2] Bardocz S, Duguid TJ, Brown DS, The importance of dietary polyamines in cell regeneration and growth, *Br J Nutr*, 1995, 73, 819-28

[3] Löser C, Polyamines in Human and animal milk, *Br J Nutr*, 2000; 84 (Suppl. I): 555-8

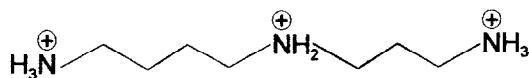
Thus, the quantity of spermidine that will be consumed per day in the dietary supplement: 0.143 to 0.285 mg (equivalent to 0.25 - 0.50 mg of the trihydrochloride salt) is consistent with the concentration range found in food.

### Free base – salt interconversion

Spermidine is an organic base, with three amino groups that naturally react with acids to form salts. Upon ingestion, spermidine is exposed to the acidic gastric medium of the stomach, which has a pH of approximately 1.0 due to the physiological presence of 0.1 N HCL. This causes the Spermidine to convert naturally and quantitatively into the trihydrochloride salt form, regardless of whether the free base or any salt form was initially ingested. Thus, the safety profile of spermidine trihydrochloride should be the same as free spermidine.

Once dissolved into body fluids, Spermidine is converted to and remains in a salified, or “protonated,” form. The acidic-basic equilibrium of the body fluids establishes and maintains the protonated form:





Once dissolved and salified, the protonated form may couple with any negatively charged counter-ion. These negatively charged counter-ions originate from organic or inorganic acids present in the body (e.g. chloride ions) that are present as physiological substances throughout the body.

### Safety Review



### Clinical trials

The efficacy of two different food supplements, both administering 0.5 mg of spermidine trihydrochloride per day, were studied in two clinical trials. An analysis of the adverse events reported in those trials further supports the safety of the ingredient.

#### First trial

The first is a double blind, placebo controlled, clinical trial performed on 60 healthy and compliant subjects, men and women, aged 18-60 (attachment B).

The product under investigation was in the form of hard gelatine capsules.

Among the subjects who took spermidine, three subjects reported moderate pyrosis after taking the capsules, this problem was overcome by taking the supplement at meal time. One subject reported worsening of IBS condition (irritable bowel syndrome) with diarrhea after he took the capsule: this side effect disappeared spontaneously after the subject had taken the fourteenth capsule and did not result in the subject dropping the study. Two subjects taking the placebo reported moderate pyrosis after taking the capsule presumably due to its gelatine shell. Even in this case, they took the capsule at meal time and the problem was overcome.

#### Second trial



**Market experience in Europe**

A food supplement containing 0.5 mg of spermidine hydrochloride per tablet, called 'Bioscalin Retard with Biogenina', was introduced into the Italian market, by Giuliani SpA, in March 2003.



**Conclusion**

Based on the information above and included herein, we conclude that spermidine trihydrochloride, when used under the conditions recommended in the labelling of the dietary supplement, will reasonably be expected to be safe.

Respectfully

GIULIANI S.p.A.

By: 

Dr. Sergio Baroni  
Regulatory Affairs