



**Memorandum**

0436 '03 JAN 27 P2:24

Date:   
From: Consumer Safety Officer, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821  
Subject: 75-Day Premarket Notification of New Dietary Ingredients  
To: Dockets Management Branch, HFA-305

Subject of the Notification: *Uridine*  
Firm: *Amino GmbH*  
Date Received by FDA: *August 30, 2002*  
90-Day Date: *November 28, 2002*

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.

*Angela F. Pope*  
Angela F. Pope  
Consumer Safety Officer

Attachments

95S-0316

RPT 153

TELEFAX

Seite 1

AMINO GmbH - Postfach 20 - 38373 Frelstedt / Germany

Telefax 0 53 55 / 899-222 - Telefon 0 53 55 / 899-123



FDA, College Park/ MD  
Division of Standards and Labeling Regulations (DSL.R)  
Mrs. Felicia B. Satchell, Director

Fax-No.: 001 301/ 436-2636

Frelstedt, Nov. 13, 2002  
Dr. S.

**New Dietary Ingredient Notification - Uridine**

Dear Mrs. Satchell,

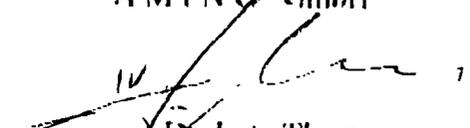
thank you for your response to our submission of a new dietary ingredient notification per fax of Friday, Nov. 08, 2002 which we received on Monday, Nov. 11, 2002.

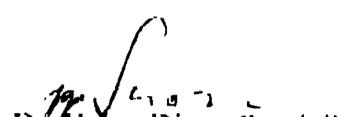
We have noted that the information we have submitted to you is incomplete and does not provide the necessary minimum requirements. Corrections could be done before Nov. 13, 2002 otherwise it is possible to send you a new notification that fully complies with 21 CFR 190.6. Due to the short period of time for corrections we will file a new notification and submit it to you.

Thank you for your attention.

Yours sincerely,

AMINO GmbH

  
Dr. Lutz Thomas  
Sales and Marketing Manager

  
Dr. Heinz-Dieter Smolnik  
QM/ GMP Manager



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
College Park, MD

NOV 8 2002

Dr. Lutz Thomas  
Dr. Heinz-Dieter Smolnik  
AminoGmbH  
An der Zucker-Raffinerie 10  
38373 Frellstedt Germany

Dear Dr. Thomas and Dr. Smolnik:

This is in response to your submission of a new dietary ingredient notification, dated August 26, 2002, to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2) and 21 CFR 190.6. FDA received and filed your notification on August 30, 2002, of your intent to market the product Uridine.

In accordance with 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains 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 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new 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 deemed 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.

Your submission indicates that you intend to market Uridine at suggested daily doses of up to two grams a day. Your submission also contains information that you believe establishes that the new dietary ingredient Uridine, when used under the condition recommended or suggested in the labeling will reasonably be expected to be safe. However the information in your submission is incomplete and does not provide the minimum information required by 21 CFR 190.6 (copy enclosed). You may also view FDA's web site at <http://www.cfsan.fda.gov/~cims/ds-ingrd.html> for additional details on new dietary ingredient notification requirements.

For example, the notification you sent us concerning Uridine does not comply with the requirements of 21 CFR 190.6 because it fails to:

- specify the level of Uridine that would be contained in a dietary supplement,
- specify in what form the dietary supplement will be used (e.g., tablet, powder, elixir)
- specify the conditions of use recommended or suggested in the labeling of a dietary supplement containing Uridine or the ordinary conditions of use of such a dietary supplement.

In addition, it would be helpful in our review of your notification to also identify any subgroups that should be excluded (e.g., infants, children, pregnant or lactating women, persons with certain medical conditions or those taking particular medications) along with any recommended duration of use (e.g., for a certain number of months versus every day).

If you market your product without meeting the requirements of 21 CFR 190.6, your product is adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains new dietary ingredients for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited by 21 U.S.C. 331(a) and (v).

You are welcome to send us the required information to correct the deficiencies in your current notification before November 13, 2002. If you prefer, you instead can elect to send us a new notification that is complete and fully complies with 21 CFR 190.6. Upon receipt of this information, we will revise the notification's filing date, which will be the date this office of FDA receives the additional information. Please see the enclosed reference for our mailing address.

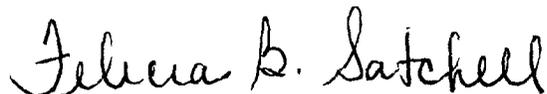
Your notification will be kept confidential for 90 days after the filing date. After November 28, 2002, the notification and related correspondence from FDA will be placed on public display at FDA's Documents Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information that is in the notification will not be disclosed to the public. Prior to November 28, 2002, you may wish to identify in writing specifically what information you believe is proprietary in your current notification.

Dr. Lutz Thomas and Dr. Heinz-Dieter Smolnik

for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notification should be redacted before it is posted at Eockets.

If you have any questions concerning this letter, please contact me at (301) 436-2371.

Sincerely yours,



Felicia B. Satchell

Director

Division of Standards,

and Labeling Regulations

Office of Nutritional Products, Labeling

and Dietary Supplements

Center for Food Safety

and Applied Nutrition

Enclosure



AMINO GmbH - Postfach 20 - 38373 Frellstedt

**U.S. Food and Drug Administration  
Center for Food Safety and Applied Nutrition, CFSAN  
Office of Nutritional Products, Labeling, and Dietary Supplements  
HFS-820  
Division of Standards and Labeling Regulations  
Attn.: Ms. Margaret C. Carlson, Acting Team Leader  
5100 Paint Branch Parkway  
College Park, MD 20740-3835  
USA**

Your reference

Our reference  
Dr. Tms/ SCH

Telephone  
+49 53 55/ 6 99 - 1 24

Date  
Aug. 26, 2002

**New Dietary Ingredient Notification - Uridine**

Dear Ms. Carlson,

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, AMINO, located at 'An der Zuckerraffinerie 10' in 38373 Frellstedt/ Germany, submits this new dietary ingredient notification to the Food and Drug Administration ("FDA") for Uridine to be manufactured by AMINO.

AMINO's Uridine product is intended for use as a dietary ingredient in dietary supplements. The product was critically evaluated by a panel of independent recognized experts. The panel unanimously concluded that under the conditions of intended use as a dietary ingredient in dietary supplements, AMINO's Uridine product, meeting food grade specifications and manufactured in accordance with current good manufacturing practices, would not present a significant or unreasonable risk of illness or injury, and would reasonably be expected to be safe.

Attached is a discussion of the scientific data and information demonstrating that AMINO's Uridine product, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. Included in the attachment are the following:



Amino GmbH  
An der Zuckerraffinerie 10  
38373 Frellstedt / Germany  
Telefon 05355 / 699-0  
Telefax 05355 699-222  
E-mail AMINO@f-ho1.de.de

Geschäftsführer  
Dr.-Ing. Jürgen Thomme  
Reg. stegergericht  
Helmstedt: HRB 1069  
Ust-IdNr: DE 114 883 641  
Internet: www.amino.de

Deutsche Bank AG Helmstedt  
(BLZ 27070043) Konto-Nr. 8010159

DG Bank Hannover  
(BLZ 25060000) Konto-Nr. 0000011000



AMINO GmbH - Postfach 20 - 38373 Frelstedt

**U.S. Food and Drug Administration  
Center for Food Safety and Applied Nutrition, CFSAN  
Office of Nutritional Products, Labeling, and Dietary Supplements  
HFS-820  
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Attn.: Ms. Margaret C. Carlson, Acting Team Leader  
5100 Paint Branch Parkway  
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USA**

Your reference

Our reference  
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Telephone  
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Date  
Aug. 26, 2002

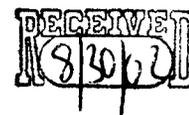
**New Dietary Ingredient Notification - Uridine**

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Amino GmbH  
An der Zucker-Raffinerie 10  
38373 Frelstedt - Germany  
Telefon 05355 1 699-0  
Telefax 05355 699-222  
E-mail: AMINO@t-online.de

Geschäftsführer  
Dr.-Ing. Jürgen Thommel  
Registriergericht  
Helmstedt HRB 1069  
Ust-IdNr. DE 114 883 641  
Internet: www.amino.de

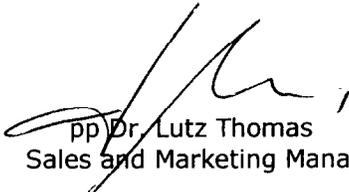
Deutsche Bank AG Helmstedt  
(BLZ 27070043) Konto-Nr. 8010159  
DG Bank Hannover  
(BLZ 25060000) Konto-Nr. 000-0-04075t.

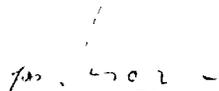


- (1.0) chemistry, manufacturing and
- (2.0) a description of the proposed use, and
- (3.0) safety data, and
- (4.0) a conclusion, and
- (5.0) a list of references.

Sincerely,

**AMINO GmbH**

  
pp Dr. Lutz Thomas  
Sales and Marketing Manager

  
pp Dr. Heinz-Dieter Smolnik  
QM/ GMP Manager

Enclosures

- Expert Panel Opinion Statement: The Safety of Uridine Dietary Supplement Product  
Manufactured by AMINO
- Copy of cited references



## Uridine Documentation

### Content

<b>Enclosure</b>	<b>Title</b>
Expert Panel Opinion Statement: The Safety of Uridine Dietary Supplement Product Manufactured by AMINO	
1	A critical evaluation of the available information on the toxicity/ safety of orally administered Uridine – by Joseph F. Borzelleca (June 2002)
2	Material Safety Data Sheet for Uridine
3	Uridine Toxicity – by Dr. Vincenzo Politi (March 2002)
4	Curriculum vitae of Dr. Vincenzo Politi
Copy of cited references	
5	List of references (acc. to Enclosure 1 - Joseph F. Borzelleca)
6	List of references (acc. to Enclosure 3 - Dr. Vincenzo Politi)
7	Document of the sworn translator Ms. Karin Wirth (Italian translations)
8	Document of the sworn translator Mr. Horst Petermann (German and Russian translations)

Professor Emeritus  
Pharmacology & Toxicology  
Medical College of Virginia



President  
Toxicology and Pharmacology, Inc.  
Consultative Services

8718 September Drive, Richmond, VA 23229-7319 U.S.A.

Tele: 804.285.2004

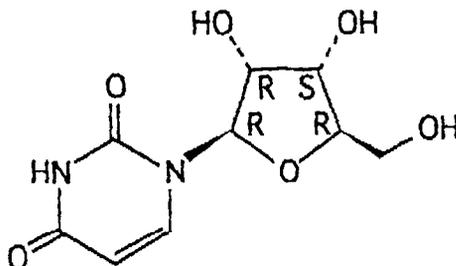
Fax: 804.285.1401

Email: toxpro@aol.com

A Critical Evaluation of the Available Information on the Toxicity/Safety  
of Orally Administered Uridine

The available safety information on orally administered Uridine is very limited. A comprehensive search of the Scientific Literature conducted by Dr. George A. Burdock failed to identify significant toxicity studies. The literature search, information provided by Dr. Lutz Thomas which included information on the characterization of uridine, manufacturing process, specifications and batch analyses, pharmacological effects, clinical studies and safety information (from Polifarma), and other materials deemed appropriate were critically evaluated to assess the safety of Uridine as a dietary supplement.

Uridine, 1-beta-D-ribofuranosyl-2, 4(1H, 3H)-pyrimidinedione, 1-beta-D-ribofuranosyl-uracil, 1-beta-D-ribofuranosyluracil (CAS Registry Number: 58-96-8 and E.C. number: 200-407-5) and with an empirical formula, C<sub>9</sub> H<sub>12</sub> N<sub>2</sub> O<sub>6</sub> and a structural formula,

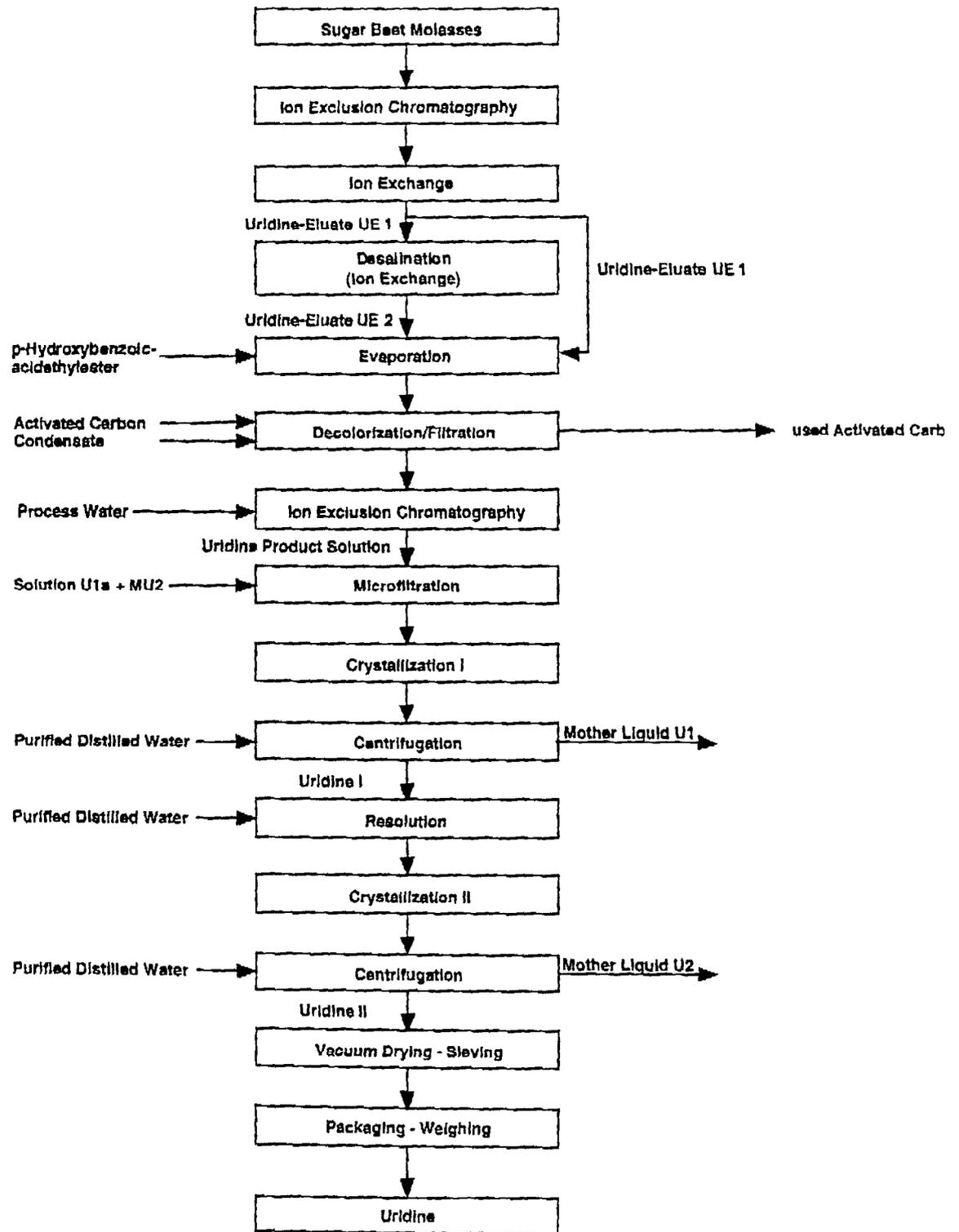


is a nucleoside that is widely distributed in nature.

It is synthesized in the body and is involved in a number of biochemical reactions. For example, it is phosphorylated to form UMP (uridine monophosphate) and UDP (uridine diphosphate) which is then ultimately incorporated into DNA or it may be further phosphorylated to form UTP (uridine triphosphate) which may be synthesized into RNA or it may be involved in protein glycosylation or cellular membrane formation. Uridine is metabolized to uracil, which enters the tricarboxylic acid cycle by way of beta-alanine formation.



The following process using current Good Manufacturing Practice manufactures uridine.





The specifications for Uridine include the following:

Parameter	Limit
Appearance: White or almost white, crystalline powder	Passes
Identification	Passes
Transmittance (1% (m/V) in H <sub>2</sub> O)	> 98.0%
Test on turbidity (10% (m/V) in H <sub>2</sub> O)	≤ Ref. Sups. I
Test on color (10% (m/V) in H <sub>2</sub> O)	≤ BG <sub>6</sub>
Chlorides	≤ 200 ppm
Sulfates	≤ 300 ppm
Ammonium	≤ 200 ppm
Iron	≤ 10 ppm
Heavy metals (as Pb)	≤ 10 ppm
Loss on drying	≤ 0.5%
Residue on ignition	≤ 0.1%
Assay	98.5 to 101.0%
Total viable aerobic count	≤ 1000 CFU/g
Molds and yeasts	≤ 100 CFU/g
Escherichia coli	in 1 g n.n.
Salmonella species	in 1 g n.n.
Pseudomonas aeruginosa	in 1 g n.n.
Staphylococcus aureus	in 1 g n.n.



The following batch analyses confirm the consistency of Uridine manufactured by the process described above.

Lot	721000010	721000020	721000030
Description	White or almost white crystalline powder	White or almost white crystalline powder	White or almost white crystalline powder
Identity	Passes	Passes	Passes
Test on turbidity	Passes	Passes	Passes
Test on turbidity	Passes	Passes	Passes
Chloride (Cl)	Not more than 200 ppm	Not more than 200 ppm	Not more than 200 ppm
Ammonia (NH <sub>4</sub> )	Not more than 200 ppm	Not more than 200 ppm	Not more than 200 ppm
Sulfate (SO <sub>4</sub> )	Not more than 300 ppm	Not more than 300 ppm	Not more than 300 ppm
Iron (Fe)	Not more than 10 ppm	Not more than 10 ppm	Not more than 10 ppm
Heavy metals (as Pb)	Not more than 10 ppm	Not more than 10 ppm	Not more than 10 ppm
Loss on drying	0.03%	0.02%	0.04%
Residue on ignition	0.03%	0.03%	0.04%
Assay (HPLC)	100.5%	99.8%	100.2%
Total microbial count	Not more than 1000 CFU/g	Not more than 1000 CFU/g	Not more than 1000 CFU/g

Some reported clinical indications and recommended doses include anti-arthritic, 1-5 mg/day; analgesic, 1.25-5.0 mg/day; neuropathies and polyneuropathies, 9-900 mg/day; CNS depression (sedative, anti-epileptic, neurological disorders, dysfunctional dopaminergic disorders); neurodegenerative disorders (for example, dementia, Parkinsonism, MS, ALS), 10 mg to 10 grams; following FU therapy, 1-12 g/m<sup>2</sup> [~24 grams], i.v. /day; orotic aciduria, 200 mg/day.

The acute oral toxicity of Uridine is extremely low, LD<sub>50</sub> >10 g/kg in mice and rats (Peterson, I. et al, 1987); Politi, V. (2002) reported acute oral LD<sub>50</sub> > 4 g/kg in mice and rats. There were no consistent compound-related dose-dependent adverse effects reported in the following oral toxicity studies: 30-day repeated dosing study in rats at doses of 166 or 500 mg/kg bw/day; 30-

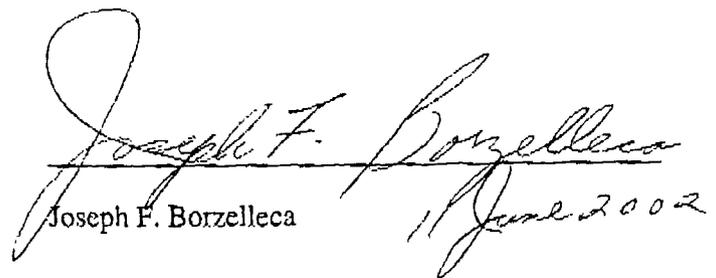
day repeated dosing study in rabbits at doses of 104 or 208 mg/kg bw/day; 120-day study in rats at doses of 83 to 250 mg/kg bw/day; 120-day repeated dosing study in dogs at doses of 104 to 250 mg/kg bw/day (Politi, V. 2002). There were no reported adverse effects on fertility, embryo genesis and peri-post natal development in rats and rabbits at oral doses of 50 to 416 mg/kg bw/day (Politi, V., 2002).

There are a number of human studies involving Uridine administration after 5-FU. Uridine was also investigated in healthy volunteers (Politi, V. 2002). For example, in the study by van Groeningen, et al (1991), Uridine was orally administered to six healthy volunteers and nine patients with metastatic colorectal cancer. It was reported "Oral Uridine was studied as single-dose administrations at doses escalating from 0.3 to 12 g/m<sup>2</sup> and as multiple-dose administrations every 6 hours for 3 days at doses from 5 to 10 g/m<sup>2</sup>. The maximum tolerated dose was 10-12 g/m<sup>2</sup> for a single dose of Uridine and 5 g/m<sup>2</sup> (approximately 10 grams per day) for the multiple-dose regimen. Diarrhea was the dose-limiting toxic effect." [The total body surface for an adult male is 1.94 m<sup>2</sup> and for an adult female, 1.69 m<sup>2</sup>, U.S. E.P.A., 1989]. In his critical evaluation of the available information, published and unpublished, on Uridine, Politi (2002) concluded that "Uridine is a rather safe drug in humans at least at doses up to 10 grams: side effects over this limit appear as fever and shivering [presumably due to the accumulation of beta-alanine, a metabolite of uracil which is a metabolite of Uridine] (by i.v. injection), and as diarrhea (by oral route)." He further notes "Uridine has been used for more than 30 years in Italy on several hundred thousand people, at doses up to 300 mg/day for several months, without reports of side effects. Moreover, small groups of children affected by Orotic aciduria are treated daily with very high doses of Uridine (200 mg/kg) for many years, without evidence of toxic effects."

It may be concluded from the above that the oral toxicity of Uridine is extremely low. For example, dogs tolerated doses of 250-mg/kg bw/day for 120 days, there was no evidence of reproductive or developmental toxicity at doses up to 416-mg/kg bw/day, and it was not genotoxic. The only side effect reported in humans was diarrhea at daily oral doses greater than approximately 10 grams/day. This is a self-limiting side effect. It may be further concluded that Uridine, at suggested daily doses of up to two grams per day as a dietary supplement, should not elicit adverse health effects.

Uridine at suggested daily doses of up to two grams/day as a dietary supplement should be safe for children and adults.

It is concluded from a critical evaluation of available information that Uridine at daily doses up to two grams should not elicit adverse health effects.

  
Joseph F. Borzelleca  
June 2002

## References

- Connolly, G.P. et al. (1999) Uridine and its nucleotides: biological actions, therapeutic potentials. *TiPS* **20**, 218-225.
- Cornford et al. (1975) Independent blood-brain barrier transport systems for nucleic acid precursors. *Biochim. Biophys Acta* **349**, 211-219.
- EP 0348360 Polifarma S.p.A., Rome, Italy (1989) Pharmacological use of uridine in the treatment of nervous disorders.
- EP 0462075 Polifarma S.p.A., Rome, Italy (1991) Use of uridine in the pharmacological treatment of the peripheral complications of diabetes.
- „FI“ (1992) Nukleotide gegen Kreuzschmerzen [Nucleotides against low back pain]. *Therapiewoche Neurologie* **6(12)**, 797.
- Filip, K.B. (1997) Wie die Alkohol-Neuropathie in den Griff zu kriegen ist. *Z. Allgemeinmedizin* **73(9)**, 527.
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- Karkishchenko, N.N.(1990) *Farmakologija Tokskologija* **53(4)**, 67-72.
- Kimura, T. et al. (1996) N3 phenacyluridine, a novel hypnotic compound, interacts with the benzodiazepine receptor. *Eur. J. Pharmacol* **311**, 265-269
- Laurinec, K. (1987) Regeneration des peripheren Nervensystems bei Polyneuropathien. *Therapiewoche* **37**, 2393-2398.
- Merlini, G. et al. (1986) Effects of large doses of pyrimidine nucleosides cytidine and uridine in elderly patients with neuropsychological disturbances caused by vascular and cerebral metabolic insufficiency. *Gazz. Med. Ital. Arch. Sci. Med.* **145(6)**, 379-390.
- Michael, J. (1987) Treatment of spinal column syndromes in orthopedic practice. *Therapiewoche* **36(47)**, 4863-4864.
- Otsuka Pharma Co. Ltd. Japan. Purine nucleosides and pyrimidine nucleosides for the treatment of memory loss. JP09030976.
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- Roberts, C.A. et al. (1974) Uridine anticonvulsant effects: selective control of nucleoside incorporation in experimental epilepsy. *Epilepsia* **15(4)**, 479-500
- Schuppen, W. et al. (1986) Paresthesias and pain syndromes in multiple sclerosis. Therapy with a nucleotide and vitamin B combination. *Therapiewoche* **36(35)**, 3553-58 (German).

US 5,962,459 Polifarma S.p.A., Rome, Italy (1996) Therapeutic active agent for treatment of neuron degenerative diseases.

US 5190948 Polifarma S.p.A., Rome, Italy (1991) Use of uridine in the pharmacological treatment of the peripheral complications of diabetes.

Villardita, C. et al. (1983) Effects of pyrimidine nucleosides and n-acetyl-glutamine on learning and memory processes in men of various ages. *Acta Therapeutica* **9**, 407-416.

Waltzing, P. et al. (1982) Randomized double-blind trial of uridine triphosphate against placebo in idiopathic neck and back pain. *Rheumatologie* **34(4)**, 163-165.

WO 0006174 A1. Massachusetts institute of technology (1999) Methods for increasing cytidine levels in vivo and treating cytidine-dependent human diseases.

WO 0030619 Method of promoting cervical and vaginal secretions. Inspire Pharmaceutical Inc., USA.

WO 9426280. Korea Green Cross Corp, S. Korea (1994) Remedy for arthritis containing uridine as active ingredient

WO 9813047 Williams, James, W. (1998) Improved therapeutic use of 4-quinolinecarboxylic acid derivatives, in particular brequinar, by co-administration of a pyrimidine

# EU - Safety Data Sheet

Product Name: **Uridine**  
Product Code:  
Manufacturer: **AMINO GmbH**

Date: 01.12.01  
Last revision: 28.12.00

## 1. Substance/ Preparation of the substance and name of the company

### 1.1 Substance name

Uridine

### 1.2 Name and address of the manufacturer and supplier

Amino GmbH  
An der Zucker-Raffinerie 10  
38373 Frellstedt  
Germany

Tel: +49 5355/ 699 - 0  
Fax: +49 5355/ 699 - 222  
Emergency Information:  
Emergency Telephone: +49 53 55/ 699 - 0

## 2. Composition/ Information on ingredients

CAS No.: 58-96-8  
EC No.: 200-407-5  
Molecular weight: 244,2 g/mol  
Formula:  $C_9H_{12}N_2O_6$   
Chemical name: 1-beta-D-ribofuranosyluracil

## 3. Hazards identification

The present results for assessment are not applicable to a classification by hazard characteristics according to the guideline 67/ 548/ EWG and the appropriate national legislation.

## 4. First aid measures

- 4.1 General: --
- 4.2 Inhalation: Remove patient to fresh air and seek medical advice in case of irritation.
- 4.3 Skin contact: --
- 4.4 Eye contact: Rinse thoroughly with water whilst lifting eyelids.
- 4.5 Ingestion (bigger amounts): In case of indisposition seek medical advice .
- 4.6 Notes to physicians: --

Product Name:	Uridine
Product Code:	
Manufacturer:	AMINO GmbH

Date:	01.12.01
Last revision:	28.12.00

## 5. Fire fighting measures

- 5.1 Fire extinguishing media: Water, powder, foam.
- 5.2 Particular hazards: Flammable. In case of fire hazardous fumes might emerge.
- 5.3 In case of fire might emerge: Nitrogen gases.

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## 6. Accidental release measures

- 6.1 Precautionary measures: Avoid raising dust.
- 6.2 Clean up activities: Sweep up dry, dispose as waste and clean subsequently.

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## 7. Handling and storage

- 7.1 Handling: No particular requirements.
- 7.2 Storage: Dry and in tightly closed containers at room temperature.  
No particular requirements.
- 7.3 Storage class: 10 - 13

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## 8. Exposure controls and personal protection

- 8.1 Additional points for the development of technical equipment: --
- 8.2 Personal protection: Breathing protection: dustmask  
Eye protection: protective glasses  
Hand protection: not necessary  
Body protection: wearing of suitable protective clothes

Informations on working hygiene: wash hands thoroughly after contact with the material

---

## 9. Physical and chemical properties

- 9.1 Appearance:
- |         |                  |
|---------|------------------|
| Form:   | crystals         |
| Colour: | white            |
| Odour:  | nearly odourless |

Product Name: **Uridine**  
Product Code:  
Manufacturer: **AMINO GmbH**

Date: 01.12.01  
Last revision: 28.12.00

#### 9.2 Security relevant data:

Melting temperature: approx. 165 - 167 °C  
Boiling temperature: not available  
Ignition temperature: not available  
Combustion point: not available  
Explosion limits: lower not available  
                                  upper not available  
  
Density: not available  
  
Solubility in water (20°C) soluble in water  
  
Thermal decomposition: not available

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#### 10. Stability and reactivity

##### 10.1 Incompatible materials and conditions to avoid:

Strong oxidizing agents

##### 10.2 Hazardous combustion and decomposition products:

Toxic fumes of carbonmonoxide, carbondioxide, nitrogenoxides

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#### 11. Toxicological information

##### 11.1 Acute toxicity:

Classification relevant LD/LC 50 values: IPR/MUS 5.1 g/ kg of body weight

##### Primary irritation:

Ingestion of bigger amounts may *possibly* damage health. *May* cause eye irritation.

##### 11.2 Chronic effects:

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##### 11.3 Experiences on humans:

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##### 11.4 More toxic informations:

No toxic health effects known when properly handled.

##### 11.5 Other informations:

This material is to handle with necessary care as for chemicals.

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#### 12. Ecological information

At proper handling and use no ecological harms are known.

Other informations: none

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Product Name: **Uridine**  
Product Code:  
Manufacturer: **AMINO GmbH**

Date: 01.12.01  
Last revision: 28.12.00

**13. Disposal information****Product:**

There are no standardized legal requirements for the disposal of chemicals in the memberstates of the EU. In Germany is existing the KREISLAUFWIRTSCHAFTS- UND ABFALLGESETZ (KrW/ AbfG) which is regulating the utilization of waste, so there is to distinguish between „waste for utilization“ and „waste for disposal“.

Special cases – especially at the distribution – are regulated by the federal states. Please contact the relevant authorities (legal authority or waste disposal offices) where you can get informations about the utilization or disposal of waste.

**Packaging:**

Disposal according to the legal regulations. Contaminated packaging is to handle according to the substance itself. As far as there are no legal regulations, non-contaminated packaging material is to handle as domestic waste or is to recycle.

**14. Transportation information**

No hazardous material according to the transportation regulations.

**15. Regulatory information****15.1 Labelling according to the EU regulations**

The present results for assessment are not applicable to a classification by hazard characteristics according to the guideline 67/ 548/ EWG and the appropriate national legislation, therefore no hazardous symbol, labelling and R-phrases are necessary.

S-phrase: 24/25 Avoid contact with skin and eyes

**15.2 German regulations:**

Water hazardous classification: I  
Others: --

**16. Other information**

The data given herein are based on current knowledge and experience. There is no demand of completeness and the user should consider this Safety Data Sheet only as a guide.

## **URIDINE TOXICITY**

Reports on the toxicity of Uridine in literature are uncommon, both because the compound is very safe, and because it has been introduced in therapy in Italy more than 30 years ago, when requirements for toxicity by regulatory bodies were not very stringent.

Here we summarize the available reports and their sources:

### **1. Animal data published in russian:**

“Acute and chronic toxicity of uridine and inosine” by I.Petersone, S.Germane, D.Berzina, U.Mikstais (from Inst.Org.Sint., Riga, URSS). Eksp.Klin.Farmakoter. 1987, 16, 134-7: Acute toxicity studies in both mice and rats showed oral LD50 values for uridine and inosine to be > 10 g/Kg. I.v. LD50 values of both compounds were >0.5 g/Kg in both species, and i.p. toxicities were even lower. Chronic toxicity studies of uridine and inosine in dogs and rats also revealed very low toxicity.

### **2. Animal data recovered from Polifarma files:**

Polifarma performed a complete set of pharmaco-toxicological studies on Uridine and a mixture containing also Cytidine and Glutamine in 1968, prior to clinical studies on the product “Centrum”. The complete report (in italian) is still available.

From that report, and from other toxicity studies performed in more recent times (whose reports are available only as summary tables), it is possible to conclude that the LD50 of uridine is over 2 g/Kg by injection (both i.p. and i.v.) in mice and rats, and over 4 g/Kg in both species by oral route.

As regards chronic administration in rats (100 mg/Kg by oral route, and 50 mg/Kg i.p., for 180 days), no differences with controls were observed for all the considered parameters.

Similarly, no toxicity signs were detected in rats, treated with oral doses between 166 and 500 mg/Kg/day for 30 days; in rabbits orally treated with 104 or 208 mg/Kg/day for 30 days; in rats treated by oral route with 83 to 250 mg/Kg/day for 120 days; in dogs orally treated with 104 to 250 mg/Kg/day for 120 days.

Uridine had no toxic effects on fertility, embriogenesis and peri-post natal complicances in rats and rabbits at oral doses between 50 and 416 mg/Kg/day.

Finally, no toxic effects were found on blood pressure, breath, and ECG of rats, rabbits and cats treated orally or by injection up to 200 mg/Kg.

### **3. Human studies:**

Because of the pharmacological use of high doses of Uridine in the rescue therapy after administration of the anticancer drug 5-FU, several safety studies have been performed and published, describing the use of Uridine in healthy volunteers or in cancer patients.

For example, in *Cancer Research* (44, 5928-33, 1984) A.Leyva and coll. reported that "Uridine was administered at 1 hour i.v. infusion at doses of 1 to 12 g/sq m. ...In 23 courses of uridine alone, the only toxicity observed was transient shivering after one of two courses at 12 g/sq m. This side effect was also seen after administration of uridine (10 g/sq m) during combination with 5-FU". In *Cancer Treat Rep* (70, 745-50, 1986), C.J. van Groeningen and coll. referred that "Uridine administration was examined as a continuous infusion at 1 and 2.5 g/m<sup>2</sup>/hr (two patients) and as a series of intermittent infusions during 72 hours at doses of 1-3 g/m<sup>2</sup>/hr, whereby 3-hr uridine administration was alternated with 3-hr treatment-free interval (six patients). Continuous infusion of uridine was discontinued due to rapid increase in body temperature". It was later demonstrated (*Pharmaceutical Res.* 4, 113-9, 1987) that fever is due to accumulation of  $\beta$ -alanine, a metabolite of uracil. In *J.Natl.Cancer Inst.* (83, 437-41, 1991), C.J. van Groeningen and coll. studied the effects of orally administered Uridine in six healthy volunteers and nine patients with metastatic colorectal cancer: "Oral Uridine was studied as single-dose administrations at doses escalating from 0.3 to 12 g/m<sup>2</sup> and as multiple-dose administrations every 6 hours for 3 days at doses from 5 to 10 g/m<sup>2</sup>. The maximum tolerated dose was 10 to 12 g/m<sup>2</sup> for a single dose of Uridine and 5 g/m<sup>2</sup> for the multiple-dose regimen. Diarrhea was the dose-limiting toxic effect.

In conclusion, therefore, the published studies suggest that Uridine is a rather safe drug in humans, at least at doses up to 10 grams: side effects over this limit appear as fever and shiverings (by i.v. injection), and as diarrhea (by oral route).

On the other hand, Uridine has been used for more than 30 years in Italy on several hundred thousand people, at doses up to 300 mg/day for several months, without reports of side effects. Moreover, small groups of children affected by Orotic aciduria are treated daily with very high doses of Uridine (200 mg/Kg) for many years, without evidence of toxic effects.

Rome, 6<sup>th</sup> march 2002

V.Politi