



Memorandum

0133 '03 JAN 27 P2:24

Date: January 16, 2003
From: Chemist, 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: 3',4'-5,7-tetrahydroxyflavone
(Luteolin)(Lutimax)
Firm: SYNORX, Inc.
Date Received by FDA: August 13, 2002
90-Day Date: November 11, 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.


Kenneth M. P. Taylor, Ph.D.

Attachments

955-0316

RPT150



OCT 25 2002

Thomas P. Lahey
President
SYNORX
1031 Calle Trepadora
Suite D
San Clemente, California 92673

Dear Mr. Lahey:

This letter acknowledges receipt of a new dietary ingredient notification, dated August 6, 2002, submitted to the Food and Drug Administration (FDA) for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) [section 413 (a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)] and 21 Code of Federal Regulations (C.F.R.) 190.6. FDA received your submission on August 13, 2002. Your submission notified FDA that you intend to market Luteolin (3', 4' 5, 7-tetrahydroxyflavone), a flavonoid compound, as a new dietary ingredient.

Your notification further stated that luteolin will be marketed as a dietary supplement under the trade name Lutimax, with each pill containing 25 mg. Recommended use is 1 Lutimax pill taken 1-3 times per day. You also state in your submission that the luteolin that you intend to market is "... a bioflavonoid synthesized from the bioflavonoid rutin. The glycoside of quercitin is the starting material in the synthesis and is called rutin."

In accordance with 21 U.S.C. 350b(a)(2), a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient must submit certain information to FDA at least 75 days before the dietary ingredient is introduced or delivered for introduction into commerce. This information must include 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 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 new dietary ingredient 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 and injury.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing luteolin will reasonably be expected to be safe. You state in your submission that “luteolin-containing preparations have a long history.” However, your submission contains no information to support this statement nor establishes that historical use, if any, is relevant to reaching a conclusion that your product, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. Your submission contains 100 articles of published scientific literature on flavonoid compounds. These articles are both reviews and research studies and appear only to address topics such as the general chemistry, isolation, dietary sources, metabolism, and purported antioxidant properties of flavonoid compounds or on cells *in vitro*, or in one instance, two human subjects ingested 50 mg of luteolin suspended in starch solution in a single dose to assess intestinal absorption (reference 22). Such information is likely of limited utility in evaluating the safety of a dietary supplement containing luteolin. The studies supplied with the notification do not appear to be relevant to an evaluation of the safety of the luteolin product that is the subject of your notification. Your notification fails to explain the relationship between your substance and the substance used in the studies. Therefore, your notification does not meet the requirements establishing history of use or other evidence of safety when used as recommended or suggested as required by 21 CFR 190.6(b)(4).

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that luteolin or Lutimax, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient 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 under 21 U.S.C. 331(a) and (v).

Your submission will be kept confidential for 90 days from the date of receipt, and after November 11, 2002, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public. Prior to November 11, 2002, you may wish to identify in writing specifically what information you believe is proprietary.

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 Dockets.

Please contact us if you have questions concerning this matter.

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



i n c o r p o r a t e d

August 6, 2002

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

Re: New Dietary Ingredient Notification

Dear Sir / Madam:

In accordance with 21 CFR 190.6, SYNORx, Inc. d/b/a Lutimax Nutraceuticals, Inc. is hereby notifying the Food and Drug Administration that we intend to market a dietary supplement containing a dietary ingredient called Luteolin. Although it is our professional legal opinion that Luteolin has long been present in the food supply as an article used for food and will be offered as a dietary supplement ingredient in a form that has not been chemically altered from the natural occurring compound and thus is not a new dietary ingredient requiring a "new dietary ingredient notification" to the FDA, we nevertheless hereby submit a Notification for the marketing of a new dietary ingredient pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994.

1. The name and complete address of the manufacturer or distributor:

SYNORx, Inc., d/b/a Lutimax Nutraceuticals, Inc.
1031 Calle Trepadora
Suite D
San Clemente, CA 92673
USA

2. The name of the new dietary ingredient:

Luteolin

3. A description of the dietary supplement or dietary supplements that contain the new dietary ingredient including:

- a) the level of the new dietary ingredient in the dietary supplement:

25 mg per dietary supplement pill

- b) the conditions of use recommended or suggested in the labeling of the dietary supplement or, if none, the ordinary conditions of use of the supplement:

1031 Calle Trepadora, Suite D, San Clemente, CA 92673
phone [949] 492.6642 fax [949] 492.4270
www.SYNORx.com

Dietary Supplement Lutimax contains Luteolin, a bioflavonoid synthesized from the bioflavonoid rutin, present with or without other dietary supplements, in a pill form.

Luteolin (3', 4', 5, 7-tetrahydroxyflavone) is a flavonoid isolated from many plants including *Reseda luteola L.*, *Achillea millefolium L.*, *Chamomillae regetita*, *Cynara scolymus*, *Thymus vulgaris*, *Limonium sinuatum*, *Vitex rotundifolia*, *Erigeron canadensis L.*, *Sophora angustifolia*, *Satureja obovata*, *Lonicera japonica*. It is also found in *Propolis*.

Luteolin occurs naturally and is found as a component of many commonly consumed foods. Luteolin is found in many foods including artichoke leaves, broccoli, sage, and rosemary. It is most closely related in structure to quercetin. The glycoside of quercetin is the starting material in the synthesis and is called rutin.

Luteolin-containing preparations have a long history. The most common plant in the U.S. diet is the artichoke, the highest percentage source in nature is *Reseda Luteola*, commonly called Weld.

Luteolin is a yellow microcrystalline powder. It is sparingly soluble in water, but soluble in alkali.

Extracts from *Chemomillae regetita* (chamomile) and *Achillea millefolium L.* (yarrow), are rich in *Luteolin* and its glycosides. They are well established for a wide range of beneficial effects such as anti-oxidant activity. Luteolin, constituent of artichoke leaf extract, showed a concentration-dependent inhibitory activity in several models of oxidative stress. The antioxidant potential of Luteolin, measured in Trolox test, is twice stronger than that of Vitamin E. Luteolin is a significantly more potent antioxidant than the synthetic antioxidant butylated hydroxytoluene (BHT), which is generally used in oxygen sensitive processes. Luteolin has strong scavenging properties for superoxide radicals.

Luteolin is a potent physical quencher of singlet oxygen. Luteolin inhibits single strand break in DNA induced by singlet oxygen in a dose-dependent manner. Xanthine oxidase is considered to be the most prominent biological source of harmful superoxide radicals. Luteolin is a strong competitive inhibitor of xanthine oxidase, which results in a reduced formation for H₂O₂.

Recommended use: As a dietary supplement, take 1 Lutimax pill 1-3 times daily. Do not exceed the recommend dosage without the advice of a physician.

4. The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling, reasonably will be expected to be safe. This should include citations to published articles or other evidence that forms the basis for the conclusion that the ingredient is safe. References to published literature should be accompanied by reprints or copies of the references and should be in English:

GENERAL SAFETY

Toxicity of Luteolin

Luteolin is considered nontoxic.

The determination of LD50 in various animals did not show any acute toxicity.

LD 50 of Luteolin			
Animal	Route	Dose	Reference
Mouse	Intraperitoneal	>180 mg / kg	Peng, H.; Xiang, S.; Bi, Z. (1981) Yao Hsueh T'ung Pao 16(ISS 2), 11-13 Chavant, L.; Combie, H.; Crs, J. (1975) Plant. Med. Phytother. 9(4), 267-272
Rat	Intraperitoneal	411 mg/kg	Dai, L.M., Cheng, H., Li, W.P., Liu, S.Q., Chen, M.X., Xu, S.Y. (1985) Acta Anhui Med. Univ. 20, 1-3.
Rat	Intramuscular	592 mg / kg	Annui Cooperation Group, Preliminary experimental study of Aruga decumbens Thunb. against chronic bronchitis, (1973) Chin. Herb. Med. Commun. 2, 18-23
Mouse	Oral	>2500 mg / kg	Dai, L.M., Cheng, H., Li, W.P., Liu, S.Q., Chen, M.Z., Xu, S.Y. (1985) Acta Anhui Med. Uni. 20, 1-3

Enclosed please find documentation that establishes this dietary ingredient, Luteolin, when used under the conditions suggested on the label, will reasonably be expected to be safe. This documentation includes a Certificate of Analysis, Rat Toxicity Test Information and Results, and scientific studies which also reflect Luteolin's strong safety profile. Please see citation list in alphabetical order below.

Certificate of Analysis- please also note that Luteolin is manufactured in accordance with applicable FDA Good Manufacturing Practices.

Acute Oral Toxicity Study in the Rat (FHSA Method) of Luteolin by NAMSA completed on February 6, 2001.

Scientific Study Articles:

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An original and two copies of this notice are being filed. Pursuant to 21 CFR 190.6 (c), please confirm receipt of this notice. We also request that this information be kept confidential for 90 days under the provisions of 21 CFR 190.6(e).

Thank you for your attention to this matter. Please call me if you have any questions or concerns.

Very truly yours,

SYNORx, Inc. d/b/a Lutimax Nutraceuticals, Inc.



Thomas P. Lahey
President



incorporated

CERTIFICATE OF ANALYSIS

Material: Luteolin
 Chemical Name: 3',4', 5, 7- tetrahydroxyflavone
 CAS No. 491-70-3
 Chemical Formula: C₁₀ H₁₅ O₆
 Molecular Weight: 286.24
 Lot Number: 061902-4XR
 Date: July 8, 2002

<u>TEST-ASSAY</u>	<u>SPECIFICATIONS</u>	<u>RESULTS</u>
Color	Yellow-Green	It complies
Odor	Odorless	It complies
Appearance	Yellow green amorphous powder	It complies
Loss on drying	5.5 to 9.0%	5.0%
Quercetin (HPLC)	Less than 5%	Less than 1.0%
Assay (TLC)	Rf complies to standard	It complies
Assay (FTIR)	95.0 to 101.5%	98+%
Assay (HPLC)	95.0 to 103.5%	99.96

Specifications conform to NFXL (USP)

Quality Assurance

Signed by: 

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Confidential

TA004-900/S



Lab No. 00C 08676 00
P.O. No. Check# 2415
CEP No. 1882P

DUPLICATE ORIGINAL #1

STUDY TITLE:

ACUTE ORAL TOXICITY STUDY IN THE RAT

(FHSA Method)

TEST ARTICLE:

Luteolin

IDENTIFICATION NO.:

Lot: 167-20-012

TEST FACILITY:

NAMSA
California Division

SPONSOR:

TOM LAHEY
ELRAPHA, INC.
1060 CALLE NEGOCIO
SUITE B
SAN CLEMENTE, CA 92673

NAMSA
Ensuring Medical Device
Safety and Compliance™

Corp. Hdqtrs: 2261 Tracy Road, Northwood, OH 43619-1397 / 419.666.9455 / Fax 419.666.2954
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DUPLICATE ORIGINAL #1
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DUPLICATE ORIGINAL #1
SUMMARY

The test article, Luteolin, was evaluated for oral toxicity in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500. The test article was prepared in Tween 80 to a 0.16 g/ml concentration. A single dose of 5 g/kg of body weight was gavaged to 20 rats. The animals were observed for any signs of toxicity. Ten rats were euthanatized on day 14 and the remaining ten rats were allowed to continue for 28 days. Rats euthanatized at 14 and 28 days were subjected to a gross necropsy of the viscera.

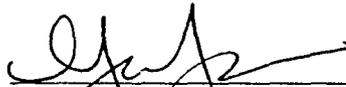
Under the conditions of this study, there was no mortality or significant evidence of toxicity observed in the rats. The 0.16 g/ml test article solution would not be considered toxic at a dose of 5 g/kg by the oral route in the rat.

Study and Supervisory

Personnel:

Gina M. Johnson, BA, LAT
Brenda Gonzalez, AS, LVT
David Vergil
Enrique Vazquez

Approved by:


Gina M. Johnson, BA, LAT
Manager, Toxicology

2-6-01
Date Completed

Study Director:


Jackie Nichols, BS
Study Director, Toxicology

2-6-01
Date Completed

/nce

DUPLICATE ORIGINAL #1
INTRODUCTION

The test article identified below was evaluated for oral toxicity in accordance with the guidelines of the Federal Hazardous Substances Act (FHSA) Regulations, 16 CFR 1500. The purpose of the study was to determine the potential for oral toxicity of the material following a single gavage in the rat. The test article was received on May 15, 2000. Animals were dosed on May 19, 2000, and the observations were concluded on June 2, 2000 and June 16, 2000.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article:	Luteolin
Identification No:	167-20-012
Storage Conditions:	Room temperature
Preparation:	With the assistance of the sponsor, a 12.8 gram sample of the test article was mixed with 80 ml of Tween 80 (Lot # H286N42468) to yield 0.16 g/ml. Duplicate mixtures were prepared, one batch for animals # 1-5 and # 11-15, a second batch for animals # 6-10 and # 16-20.

METHODS

Test System:

Species:	Rat (<i>Rattus norvegicus</i>)
Strain:	CrI:CD (SD) BR
Source:	Charles River Laboratories
Sex:	10 male, 10 female
Body Weight Range:	228 grams to 304 grams prior to fasting
Age:	No particular age was prescribed for this test
Acclimation Period:	Minimum 5 days
Number of Animals:	Twenty
Identification Method:	Ear punch

Justification of Test System:

The rat has historically been used to establish hazardous substance labeling data. The oral route of dosing is selected as the strongest challenge for materials that could be accidentally ingested.

Animal Management:

- Husbandry:** Conditions conformed to Standard Operating Procedures which are based on the "Guide for the Care and Use of Laboratory Animals."
- Food:** PROLAB® R-M-H 1000 Rodent Diet was provided daily. Food was withheld 16-20 hours prior to dosing.
- Water:** Freely available, municipal (Irvine, CA) water was delivered through an automatic watering system.
- Contaminants:** Reasonably expected contaminants in feed or water supplies did not have the potential to influence the outcome of this test.
- Housing:** Animals were housed in groups of up to five per sex in stainless steel suspended cages identified by a card indicating the lab number, animal numbers, test code, sex, animal code and date dosed.
- Environmental:** The room temperature was monitored daily. The temperature range for the room was within a range of 64-79°F.
- The room humidity was monitored daily. The humidity range for the room was 30-70%.
- The light cycle was controlled using an automatic timer (12 hours light, 12 hours dark).
- Facility:** NAMSA is an AAALAC International accredited facility and is registered with the United States Department of Agriculture. Additionally, NAMSA maintains an approved Animal Welfare Assurance on file with the National Institutes of Health, Office for Protection from Research Risks.
- Personnel:** Associates involved were appropriately qualified and trained.
- Selection:** Only healthy, previously unused animals were selected.

Experimental Procedure:

Each rat was weighed and the food was removed from each cage 16-20 hours prior to dosing. Each rat was gavaged with the test article (via stainless steel blunt-tipped cannula) at a dose of 5 g/kg of body weight. The animals were then returned to their cages and food was returned after treatment.

Animals were observed immediately after dosing, at 4 hours, and daily for up to 28 days for signs of illness or mortality. Body weights were recorded at dosing, at 14 days and at 28 days for survivors. Ten rats were euthanatized on day 14, and the remaining 10 rats were euthanatized on day 28 by carbon dioxide inhalation. Animals found dead during the study or those euthanatized (carbon dioxide inhalation) at 14 days and 28 days were subjected to a macroscopic examination of the viscera. Based on the FHSA Regulations, a substance is considered "toxic" if it produces death within 14 days in 50% of a group of rats gavaged with a single 50 mg/kg to 5 g/kg dose.

DUPLICATE ORIGINAL #1

RESULTS

Individual observations appear in Table I.

Body Weight: Body weight data were acceptable. All rats gained weight during the study.

Mortality: No animals died during the 28 day study.

Clinical Observations: On days 1 and 2, all animals were observed to have diarrhea. By day 3, the stools of all animals appeared normal. On days 1 through 5, all animals appeared to have a rough coat and yellow staining of the fur. On day 6, the yellow color of the fur began to fade. By day 9, all fur coats appeared normal. Otherwise, all animals appeared clinically normal throughout the study.

Necropsy: There were no macroscopic changes in the viscera at necropsy that could be attributed to the single oral dose.

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and EN45001 Quality Standards (TÜV Product Services 1/96).

CONCLUSION

Under the conditions of this study, the test article would not be considered toxic at a dose of 5 g/kg by the oral route in the rat.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

DUPLICATE ORIGINAL #1

TABLE IINDIVIDUAL OBSERVATIONS

Animal Number	Sex / Volume Administered (ml)*	Body Weight (g)			Clinical Observations
		Day 0	Day 14	Day 28	
1	Male / 8.8	283	382	NA	Appeared normal ^a
2	Male / 9.0	290	395	NA	Appeared normal ^a
3	Male / 8.8	284	368	NA	Appeared normal ^a
4	Male / 8.7	280	383	NA	Appeared normal ^a
5	Male / 8.1	260	356	NA	Appeared normal ^a
6	Male / 7.8	252	352	411	Appeared normal ^a
7	Male / 9.5	306	403	461	Appeared normal ^a
8	Male / 8.8	285	375	440	Appeared normal ^a
9	Male / 8.6	277	346	392	Appeared normal ^a
10	Male / 8.5	273	365	431	Appeared normal ^a
11	Female / 7.3	236	300	NA	Appeared normal ^a
12	Female / 7.3	237	298	NA	Appeared normal ^a
13	Female / 7.2	231	262	NA	Appeared normal ^a
14	Female / 7.1	228	286	NA	Appeared normal ^a
15	Female / 7.4	240	300	NA	Appeared normal ^a
16	Female / 7.1	228	280	312	Appeared normal ^a
17	Female / 6.7	216	267	300	Appeared normal ^a
18	Female / 6.8	220	262	275	Appeared normal ^a
19	Female / 6.7	217	260	291	Appeared normal ^a
20	Female / 6.9	222	270	288	Appeared normal ^a
Mean:		253	326	360	

^a All animals had diarrhea on days 1 and 3. Stools returned to normal by day 3. Fur coat ungroomed on day 1 and yellow in color on days 1-5. Fur returned to normal color by day 9.

* Dose factor - $5 \text{ g/kg} \div 0.16 \text{ g/ml test solution} = 31 \text{ ml/kg}$

DUPLICATE ORIGINAL #1

TABLE IIMACROSCOPIC EXAMINATION OF VISCERA

Animal Number	Sex	Termination	Necropsy Observations
1	Male	Day 14	Macroscopically normal
2	Male	Day 14	Macroscopically normal
3	Male	Day 14	Macroscopically normal
4	Male	Day 14	Macroscopically normal
5	Male	Day 14	Macroscopically normal
6	Male	Day 14	Macroscopically normal
7	Male	Day 14	Macroscopically normal
8	Male	Day 14	Macroscopically normal
9	Male	Day 14	Macroscopically normal
10	Male	Day 14	Macroscopically normal
11	Female	Day 28	Macroscopically normal
12	Female	Day 28	Macroscopically normal
13	Female	Day 28	Macroscopically normal
14	Female	Day 28	Macroscopically normal
15	Female	Day 28	Macroscopically normal
16	Female	Day 28	Macroscopically normal
17	Female	Day 28	Macroscopically normal
18	Female	Day 28	Macroscopically normal
19	Female	Day 28	Macroscopically normal
20	Female	Day 28	Macroscopically normal