DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date JAN 16 1998

From Acting Director, Division of Programs and Enforcement Policy, Office of Special Nutritionals, HFS-455

Subject 75-Day Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFS-305

New Dietary Ingredient:	Isopropoxy Isoflavone
Firm:	Technical Sourcing International, Inc.
Date Received by FDA:	November 19, 1997
90-Day Date:	February 22, 1998

97 784 '98 APR 30 P3:

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after February 22, 1998.

Sincerely yours,

James Tanner, Ph.D.
Acting Director,
Division of Programs and
Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and
Applied Nutrition

Attachment

cc:
HFS-22, CCO
HFS-450 (r/f, OSN w/control slip:TRAC#55844 & cpy incoming)
HFS-456 (r/f, Latham, Moore)
r/d:HFS-456:JELatham:jel:01/07/98:DocName:#55844.mem:Disc4

95S-0316

RPT22

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

Mr. Steve Lee
Technical Sourcing International, Inc.
1742 Misty Meadows
Sandy, Utah 84093

Dear Mr. Lee:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the act) dated November 19, 1997, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., Isoproproxy Isoflavone) was received by the Food and Drug Administration (FDA) on November 24, 1997. Your submission will be kept confidential for 90 days from the date of receipt, and after February 22, 1998, 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.

Please contact us if you have questions concerning this matter.

Sincerely yours,

James Tanner, Ph.D.
Acting Director
Division of Programs and
Enforcement Policy
Office of Special Nutritionals
Center for Food Safety
and Applied Nutrition

cc:
HFA-224 (w/incoming)
HFS-22 (CCO)
HFS-456 (r/f, Latham, Moore)
HFS-450 (r/f, w/ control slip OSN#55844 & cpy incoming)
f/t:HFS-456:JELatham:jel:01/07/98:DocName:#55844.OSN:Disc4

Technical Sourcing International, Inc.

1742 Misty Meadows
Sandy, UT 84093
(801) 523-2666
(801) 523-3666 FAX

1270 Avenue of the Americas
Suite 2701
New York, NY 10020
(212) 586-7764
(212) 245-2876 FAX

CERTIFIED MAIL--RETURN RECEIPT REQUIRED

TRADE SECRET: CONFIDENTIAL AND PROPRIETARY INFORMATION (Before the FDA's POST) Revised and re-submit NOV. 19, 1997

Director
Division of Program and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street
HFS-455
Washington, D.C. 20204

Dear Sir or Madam:

Notice is hereby given pursuant to the requirements of section 413(a)(2)[(21 U.S.C.350b)] of the Federal Food, Drug, and Cosmetic Act of the intent of Technical Sourcing International, Inc. to introduce a new dietary ingredient, Isopropoxy Isoflavone (the "Ingredient"), into interstate commerce 75 days after this submission. The ingredient occurs in many legume plants such as alfalfa and bee propolis. Based on the information available, we recommend a maximum daily intake of the ingredient of 600 milligrams per day. This is about 1/100 of the non-toxic daily dose performed on many animal model toxicity studies.

The following documents evidencing the ingredient are enclosed with this notice and incorporated herein by reference:

English translation of Imai K, et al., Acute Toxicity Study of Ipriflavone in Mice and Rats, Pharmacology and Therapy, Vol. 13, No. 10, 1985,p49-p54

English translation of Tokiwa T, et al., A one-year oral toxicity study of Ipriflavone on beagle dogs, Applied Pharmacology, Vol. 31, No. 1, 1986, p113-p136

Pursuant to 21 CFR section 20.60-61 Technical Sourcing International, Inc. specifically requests that this information be kept confidential and not be disclosed. Please contact me if you have any questions on this ingredient.

Thanks.

Sincerely,

Steve Lee

Steve Lee
Technical Sourcing International, Inc.

55844

A one year (fifty-two week) oral toxicity study of ipriflavone on beagle dogs

ABSTRACT:

This paper describes a one-year (52 week) oral toxicity study of ipriflavone on beagle dogs.

After 4 weeks of acclimatization, 16 male and 16 female dogs were divided randomly into four equal group. Ipriflavone was given orally in gelatin capsules at doses of 150, 500, and 1,500 mg/kg per day once daily for 52 weeks. Control animals received an empty gelatin capsule orally.

During the administration period, vomiting and discharge of abnormal feces occurred in animals of all groups, sporadically, or sometimes intermittenly. Vomiting was probably due to physical irritation of the stomach caused by administration of large amounts of test compound because the occurrence of this type of disorder is not uncommon in beagle dogs. On the other hand, the feces was mixed with blood rather frequently in 3 animals from the 1,500 mg/kg group. However, like the passage of mucous feces or diarrhea, the passage of bloody feces was probably physiological or sporadic, because the same type of disorder was seen in control animals, and because there were no histopathological changes in the gastrointestinal tract of any animals.

The test compound affected neither the body weight nor the food and water consumption.

There were no changes attributable to the drug in hematology, blood chemistry, urinalysis, organ weight, or histopathology.

The results suggest that the maximum non-toxic dose of ipriflavone for beagle dogs following one oral administration is above 1,500 mg/kg per day.

INTRODUCTION:

Ipriflavone 7-isopropoxy-3-phenyl-4H-1 benzopyran 4 one

This was introduced and provided by Takeda Pharmaceutical Company and the Hungarian Chinoin Company. This was tested jointly by these companies for abnormal bone metabolis. This experiment was completed for a 52 week oral administration period.

EXPERIMENTAL MATERIALS AND METHODS:

1. Materials Used:

Ipriflavone, 7-isopropoxy-3-phenyl-4H-1 benzopyran 4 one was acquired from Takeda pharmaceutical Company, Lot No M263-019 (100.0%), M263-020 (99.9%), M263-021 (100.2%). The material consists of a white crystal powder contained in metal containers well protected from sunlight and temperature change.

2. Animals used in experiment:

20 (twenty) beagle dogs acquired from White Eagle Labs of the U.S.A. After a four week quarantine period, sixteen dogs were chosen for use. The ages ranged from nine to ten months old. Weigh ranged from 8.3 -12.9 kg for females and 5.5-10.3 for males. Room temperatures ranged from 22-28° c and 40-70% humidity. Dogs were exposed to normal room light for 12 hours from 6:00 A.M. to 6:00 P.M. Each occupied a metal cage. Dogs were fed 500 grams of

food produced by Oriental Y East Company.

3. Method of administration:

125 mg of ipriflavone per kg of body weight was administered once dialy by gelatin capsule. The control group was fed 1% of hydroxymethyl cellulose once daily. The syrum concentration of ipriflavone metabolite was detected. Appendix 1 (p. 114) shows the toxicity response for 125, 500, 1000, 1500, and 2000 mg per kg of body weight.

4. Observation and examination:

1. General observation.

Dogs were closely observed before administration and after administration in intervals of 1/2, 2, 4, and 6 hours.

2. Body weight

Animals were weighed weekly.

3. Record of food and water intake.

Consumption of water intake was observed and recorded weekly.

4. Hematological examination.

Blood samples were taken once before the experiment and five times during course of this study in intervals of 5 13, 20, 39, and 52 weeks. RBC, WBC, Microcell Counter CC-108, hematocrit, hemogloblin, Hemogloblin Counter HB-100 were used to check RBC, WBC, p[latelet, hemogloblin count. Thromboplastin and prothrombin times were also checked. The Brecher method was used to check RET (reticular RBC ration). The Wright-Giemsa method was used to check WBC and bone marrow. EDTA-2K and sodium ascorbate were used to check prothrombin and thromboplastin times.

5. Hemotobiochemical exams were taken to check glutamic exalogcetic transaminase (GOT), gulutamic pyruvic transaminase (GPT), leucine aminopeptidase (LAP), creatine phosphokinase (CPK), cholinesterase, carbohydrates, bilirun, urea (BUN), creatinine, total lipids, total cholesterol, neutral lipids, phosphatidyl lipids, fatty acids, inorganic phosphorous, calcium, and total protein. Lactic dehydrogenase and alakanine phosphatase (ALP) were detected in heparin treated serum (Abbott VP Bichromatic analyzer) Serum sodium and serum chloride (Hitachi 775) AG ratio (A/G albumin globulin ration (Cliniscan, Helena Laboratories)

6. Urine

Urine samples were taken once before the experiment and five times during course of this study in intervals of 5 13, 20, 39, and 52 weeks. Density sodium content and chloride content of urine where checked using th Hitachi 775 and chloride counter CL-5M. Also, the Abbott VP Bichromatic Analyzer were used to check inorganic phosphorous. Fresh urine pH, protein, glucode, ketone body, urobilinogen, bilirubin were checked by BM test 8-II. The residue of RBC and WBC and epithelian cells were checked.

7. Eye ophthamofunduscopy

Eye exams were taken once before the experiment and five times during course of this study in intervals of 5 13, 20, 39, and 52 weeks. The pupils were enlarged by Mydrin and photographed by a Kowa RC-2 camera.

8. Body temperature, EKG, heartbeat, and blood pressure were taken once before the experiment and five times during course of this study in intervals of 5 13, 20, 39, and 52 weeks. Temperatures were taken through the rectum (BAT-12m, Bailey) EKG (ECG-5403) (Chrat speed 50 mm/sec, calibration: 100 mm/mV) Blood pressure (BP-203NP Japan Korin)

9. Pathological examination.

Dogs were adminstered pentobabital and blood was drained from the cervical artery. Visceral organs were examined by sight and pathological exams. The visceral organs and cerebrium, and cerebellum, pituitary, thyroid, thymus, heart, lungs, liver, spleen, pancreas, kidney, prostate, ovary, and uterus were all check by LIBROR EB-2800, EDL-100KM, Shimazu. The visceral organs, duodenun, illeum, rectum, appendix, limph, tonsils, trachea, exophagus, tongue, gall bladder were prepared in and 10% solution of formalin and 5% formalin. Some organ specimans were prepared in hematoxylin eosin (HE)

10. Statistical methodology. Bartlett 1937, Snedecor and Chochran 1967, Dunnett 1955, Krustkal and Wallis 1952.

EXPERIMENT RESULTS:

1. General observations

No changes were noticed in the frequency and amount of the feces of the control group versus the experimental group. One dog from each group vomited. Hemat urine occurred in one dog of the high dose group. Softened stool and diarrhea occurred in one dog of the middle dose group. At the 37th week, turbid iris occurred in one female dog.

2. During the experiment, no animals died

3. Body weight (see figure 1).

No significant changes were observed.

4. Food intake

There was a slight change in food consumption detected which does not affect the experiment statistics.

5. Water intake

Water intake remained stable throughout the experiment

6. Hetamtological exam. (See tables 1-3)

7. Hematobiochemical

After fifty-two weeks, two of the female dogs given a medium dose total lipids were

slightly raised. From the high dose group, one female had slightly raised cholesterol and total serum lipds. The slight raise did not present a significant change in statistics.

8. Urine examination (See table 13 and 14)

9. Eye and ophthamofunduscopy
No abnormalities were noticed in the eye examination.

10. Body temperature and heart temperature. EKG, blood pressure. On the 13th week, one female from the medium dose group was noticed to have a blockage between the ventrical and atrium of the heart. No changes were noticed in the high dose group.

The context of this study was originally written in Japanese. It was translated into English by Steve Lee and Martin Hansen.

Steve Lee 11/18/97

Martin J Hans 11/18/97