DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

MAR 31 1998 '98 APR 14 P2:31

Douglas D. Lazarus, Ph.D.
17 Winter Street
Watertown, Massachusetts 02172

Dear Dr. Lazarus:

This is in response to your letter to the Food and Drug Administration (FDA) dated October 21, 1997, concerning the safety of pokeweed mitogen used as an ingredient in dietary supplements. Your letter responded to a letter from FDA, dated September 24, 1997, to Mr. Sam Berkowitz of Advanced Plant Pharmaceuticals, Inc. regarding his submission to FDA pursuant to 21 U.S.C. 350b (section 413 of the Federal Food, Drug, and Cosmetic Act (the Act)).

In our letter to Mr. Berkowitz, FDA stated that it fundamentally disagreed with a determination made by him that a dietary supplement containing a mixture of lectins from the pokeweed plant (*Phytolacca americana)* will reasonably be expected to be safe. FDA tentatively concluded that pokeweed was a well-characterized poisonous plant and that toxicity to humans and animals was associated with exposure to all parts of the pokeweed plant, and that the lectins contained in pokeweed were believed to be one of primary biochemical contributors to pokeweed toxicity. FDA advised Mr. Berkowitz that his submission did not meet the requirements in 21 U.S.C. 350b and that introduction of this product into interstate commerce was prohibited under 21 U.S.C. 331(v) and that a dietary supplement containing his proposed new dietary ingredient would be subject to regulatory action pursuant to 21 U.S.C. 342(f)(1)(B)

FDA has considered the information presented in your letter and is not persuaded to change its tentative conclusion that pokeweed mitogen, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. Therefore, introduction or delivery for introduction of a dietary supplement containing pokeweed mitogen into interstate commerce is prohibited under 21 U.S.C. 331(v) and a dietary supplement containing this proposed new dietary ingredient would be subject to regulatory action pursuant to 21 U.S.C. 342(f)(1)(B)

955-0316

SUP 1

Please contact us if you have any questions concerning this matter.

Sincerely,

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

Copy:

Mr. David Berkowitz
Advanced Plant Pharmaceuticals, Inc.
17 John St., 3rd Floor
New York, NY 10038

cc:
HFA-224 (w/incoming)
HFA-305 (Docket No. 95S-0316)
HFS-22 (CCO)
HFS-308 (Bolger, Wagstaff)
HFS-456 (r/f, File)
HFS-450 (r/f, File)
r/d:HFS-456:RMoore:3/20/98
Init:GCF-1:DDorsey:3/20/98
f/t:rjm:HFS-456:3/20/98:docname:55498.osn:disc27

October 21, 1997

James T. Tanner, Ph.D.
Acting Director
Division of Programs and
Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and Applied
Nutrition
Department of Public Health Services
Food and Drug Administration
Washington, D.C. 20204

Dear Dr. Tanner:

Thank you for your response to the letter from Advanced Plant Pharmaceuticals, Inc., in New York City, which described the inclusion of pokeweed mitogen in a dietary supplement. I am writing on behalf of APPI, consulting with them on a joint project to develop a dietary supplement which contains this lectin. I have gained much experience studying lectins over the past few years, e.g., Lazarus et al., *Int J Immunopharmac* 19:48, 1997; Solorzano et al., *J Immunol* 158:414, 1997. Another paper on which I am an author, "The metabolic effects of pokeweed mitogen in mice", will be published in *Metabolism* in the next few months.

I would like to respond to your rejection of APPI's proposal to include pokeweed mitogen in a dietary supplement. You are correct in your assessment that pokeweed is a dangerous plant, and your concerns that APPI omitted the dosage of pokeweed mitogen to be added to their dietary supplement are understandable. Nevertheless, the use of pokeweed mitogen would not pose a threat to the consumer. In presenting the reasons for this, I will include excerpts from your letter.

1. "Your submission does not provide information about the quantity of the new dietary ingredient in the dietary supplement nor about the conditions of use recommended or suggested in the labeling of the dietary supplement."

The amount of pokeweed mitogen to be added to a supplement is 10mg per total daily use. Ingestion of the plant at this low dose would not be dangerous (Barker et al. *Clin Res* 15:271, 1967). The product APPI is developing, of which pokeweed mitogen is only one ingredient of many, is intended as a diet product.

2. "FDA fundamentally disagrees with your determination that a dietary supplement containing a mixture of lectins from the pokeweed plant will reasonably be safe... Toxicity to humans and animals is associated with exposure to all parts of the pokeweed plant and these lectins are believed to be one of the primary biochemical contributors to pokeweed toxicity."

I have not found in the literature where the lectins from pokeweed are believed to be one of the primary biochemical contributors to pokeweed toxicity. A detailed article (Roberge *et al.*, Ann Emerg Med, 15:470, 1986) regarding the toxicity of the pokeweed plant describes several small molecules - glycosides - with cardioactive and irritant effects. These agents are indicated by the authors as being the causes of GI disturbances that follow pokeweed ingestion. The only effects noted regarding pokeweed mitogen is that it promotes the division of white blood cells and the stimulation of interferon. The effects of the mitogen are identified only as diagnostic evidence, rather than of pathological relevance.

3. "Signs and symptoms of pokeweed poisoning include stomach cramping, nausea, bloody, persistent and debilitating vomiting and diarrhea, dyspnea, spasms, hypotension, heart block, convulsions and death."

The GI disturbances are attributed to the saponin content of the plant, not to the lectins (Roberge *et al.*, *Ann Emerg Med*, 15:470, 1986; Hamilton *et al.*, *Vet Human Toxicol* 37:66, 1995). In addition, pokeweed contains phytolaccotoxin and phytolaccine, which are potential poisons (Roberge *et al.*, *Ann Emerg Med*, 15:470, 1986).

Heart block is stated as being not due to the lectins, but rather, to the saponins (Roberge *et al.*, *Ann Emerg Med*, 15:470, 1986) or the response to severe GI colic (Hamilton *et al.*, *Vet Human Toxicol* 37:66, 1995).

The use of pokeweed mitogen as a model of brain injury has been proven incorrect by the group that studied it most closely (Kuniaki *et al.*, *J Biol Chem* 268:15496, 1993). According to that group, the only effect of pokeweed mitogen was stimulaton of immune cells and circulating levels of the markers studied (tryptophan metabolites and interferon) were increased solely because of this stimulation.

4. "Oral, ocular, and dermal exposure to pokeweed plant have been shown to result in human poisonings."

One of the groups which studied the effects of pokeweed mitogen in humans did note that plasma cells were seen in the peripheral circulation whether the plant was ingested or by exposure of open wounds to the plant juice. This group also stated `No distinctive clinical features were seen in association with the blood changes.' and `...no long term lines have originated from the transformed lymphocytes.' (Barker *et al.*, *Pediatrics* 38:490, 1966). Further, `No

symptoms, organomegaly, adenopathy, or other clinical signs were apparent [after pokeweed plant ingestion] (Barker *et al.*, *Clin Res* 15:271, 1967).

Lectin administration to mice has not shown any toxicity in the literature. To quote again: `These results indicate that pokeweed mitogen has no toxic effect at the doses given (up to 55mg/kg, Lozzio and Comas, *Int. Arch. Allergy*, 36:266, 1969).' That study was limited to immune effects of pokeweed lectins, but examined the spleen, lungs, liver and kidney organ systems.

A more recent series of animal studies in which I participated did not find any adverse effects over 16 days of treatment with pokeweed mitogen, neither behavioral nor on gross necropsy (Lazarus *et al.*, *Metabolism*, in press). This group also looked at a serum liver enzyme level (AST) and found no elevation after mice received 15mg/kg (unpublished findings).

In summary, there is no evidence that pokeweed mitogen is a poison. We believe that it falls within the definitions of the FDA guidelines and can safely be added to a dietary supplement. Thank you for your attention to this matter.

Sincerely,

Douglas Lazarus

Douglas D. Lazarus, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

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To Doug Lazarus	From [illegible]
Co.	Co.
Dept.	Phone #
Fax #	Fax #

Mr. Sam Berkowitz
Advanced Plant Pharmace
17 John Street, 3rd Floor
New York, New York 100

Dear Mr. Berkowitz:

This is in response to your letter to the Food and Drug Administration (FDA) dated July 29, 1997, making a submission pursuant to section 413(c) of the Federal Food, Drug, and Cosmetic Act (the act) for a new dietary ingredient. Your letter notified FDA of your intent to market a dietary supplement containing a new dietary ingredient that is a mixture of proteins of the type known as lectins from the pokeweed plant, *Phytolacca americana*.

Section 413 of the act requires a manufacturer or distributor of a dietary supplement which contains a new dietary ingredient to submit certain information to the agency. Specifically, the act requires that at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient provide the FDA with information which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

You have not provided 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. Your submission does not provide information about the quantity of the new dietary ingredient in the dietary supplement nor about the conditions of use recommended or suggested in the labeling of the dietary supplement. In the absence of such information, it is not possible to determine whether a dietary supplement containing this new dietary ingredient will reasonably be expected to be safe. A dietary supplement that contains a dietary ingredient that is 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 is adulterated under section 402(f)(1)(B) of the act.

FDA fundamentally disagrees with your determination that a dietary supplement containing a mixture of lectins from the pokeweed plant (*Phytolacca americana)* will reasonably be expected to be safe. Pokeweed is a well-characterized poisonous plant. Toxicity to humans and animals is associated with exposure to all parts of the pokeweed plant and the lectins are believed to be one of primary biochemical contributors to pokeweed toxicity. Oral, ocular, and dermal exposure to pokeweed plant have been shown to result in human poisonings.

Signs and symptoms of pokeweed include stomach cramping; nausea, bloody, persistent, and debilitating vomiting and diarrhea, dyspnea, spasms, hypotension, heart block, convulsions, and death.

Since you have not complied with section 413 of the act and shown that the dietary supplement that is the subject of your notification is safe, introduction of this product into interstate commerce is prohibited under section 301(u) of the act. Moreover, the dietary supplement is subject to regulatory action pursuant to section 402(f)(1)(B) of the act.

Sincerely yours,

James Tanner

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