

Expert Opinion Letter

Evaluation of the Generally Recognized as Safe (GRAS) Status of Phase 2[®] White Bean (*Phaseolus vulgaris*) Extract

The undersigned, recognized Experts (hereinafter "Experts"), qualified by scientific training and relevant international experience to evaluate the safety of food and food ingredients, were requested by Pharmachem Laboratories, Inc. to assess the safe use of Phase 2[®], also known as Phaseolamin 2250[®], Phase 2 Starch Neutralizer[™] and StarchLite[™], a standardized extract derived from the common white bean (*Phaseolus vulgaris*) that has been shown to inhibit the activity of the digestive enzyme α -amylase. Alpha-amylase is an enzyme found in plants, animals, and microorganisms that catalyzes the hydrolysis of complex carbohydrates into simpler saccharides such as maltose and glucose that can be readily absorbed. Inhibition of human α -amylase may promote weight loss by hindering the digestion of complex carbohydrates, thereby reducing the absorption of carbohydrate-derived calories.

Pharmachem Laboratories, Inc., hereafter referred to as Pharmachem, wishes to establish by scientific procedures that the use of Phase 2[®] for nutritive value, by impairing carbohydrate digestion, is self-affirmed to be Generally Recognized as Safe (Self-GRAS) as a dietary supplement and for general addition to all foods for which no defined standard of identity exists. Self-GRAS was previously established for use at levels providing up to an aggregate intake of 6 g of Phase 2[®] per day from dietary supplement and food use applications. A greater upper aggregate intake is now proposed, allowing 10 g of Phase 2[®] per day from dietary supplement and food use applications.

Initial self-GRAS determination for the Phase 2[®] product was based on the weight of the information provided in a comprehensive report prepared by CANTOX U.S. Inc., to assist the Experts. This report was a compilation of documentation supporting the safety of Phase 2[®] under the intended conditions of use. The Experts independently and critically evaluated the report and other materials deemed appropriate, and conferred by telephone.

The following summary basis for the discussion of GRAS status was provided in the report and evaluated by the Experts:

- The source material of the Phase 2[®] aqueous extract, the common white kidney bean (*Phaseolus vulgaris*), possesses a long history of safe use in the human diet when cooked and eaten as food;
- Phase 2[®] manufacturing process is well controlled and yields consistent product quality;

- The chemical composition of Phase 2[®] is well characterized. Product specifications have been provided as well as evidence supporting reproducibility;
- Preclinical safety data for Phase 2[®] indicates an absence of toxicity in rodents exposed to oral doses up to 2500 mg/kg/day for 28 days or 1112 mg/kg bw/day for 90 days (maximum dose tested);
- Clinical efficacy evaluations indicate an absence of adverse health effects in human subjects ingesting up to 3000 mg/day in divided doses with meals for periods from 30 days to 24 weeks;
- Safety concerns regarding the presence of phytohemagglutinins, naturally occurring anti-nutritional and potentially toxic substances, are addressed. Hemagglutinating activity (HA) and trypsin-inhibiting (TI) activity are heat-inactivated by processing, while preserving substantial α -amylase inhibiting activity. Intake from general food use application is within the range of normal dietary intake from other sources and there is no expectation of risk to the safety of consumers of the Phase 2[®] product;
- Given a 12:1 ratio in concentrating the aqueous Phase 2[®] extract from its source, the white kidney bean, and assuming all other trace contaminants present in the beans were concentrated into the Phase 2[®] fraction, then consuming 10 grams of Phase 2[®] would entail exposure to these microcontaminants equal to consumption of approximately 120 grams of dry beans.
- Phase 2[®] is currently used in amounts up to 4500 mg daily in products marketed worldwide under approximately 200 brand names, with no reports of adverse events.

The Experts agreed that the long-time presence of *Phaseolus vulgaris* in the human diet and its digestion by normal physiological pathways is supporting evidence of the safety of Phase 2[®]. Also supportive is its current widespread use in dietary supplements, with no known adverse events. To supplement this evidence, Pharmachem conducted a series of studies.

The results of pivotal nonclinical safety studies indicate that Phase 2[®] and dietary supplements containing Phase 2[®] is of low toxicological concern. In rats, single oral doses of up to 5000 mg Phase 2[®] per kg body weight did not result in any mortality or clinical signs of toxicity¹. Moreover, the results of a subacute GLP-compliant 28-day study demonstrated an absence of adverse effects in rats at the highest dose level, with an established No Observed Effect Level

¹ Harikumar, KB, Jesil, AM, Sabu, MC, Kuttan, R. 2005. A preliminary assessment of the acute and subchronic toxicity profile of Phase 2: An α -amylase inhibitor. *Int J Toxicol* 24:95-102.

(NOEL) of at least 2,500 mg/kg/day for administration of Phase 2[®] by oral gavage². These results are consistent with the safety of a human oral intake considered here of up to approximately 10,000 mg Phase 2[®] per person per day (*i.e.*, 142.9 mg/kg/day assuming a 70 kg human) and represent a 17.5-fold exposure safety factor. The highest dose given to rats in this study (2,500 mg/kg/day) would be equivalent to approximately 175 g/day in a 70-kg person, or 17.5-fold the proposed upper limit of aggregate intake of 10 g per day from dietary supplement and food use applications.

The results of a earlier subchronic toxicity study in rats revealed no variations that could be attributed to treatment with Phase 2[®] at doses up to 1,000 mg/kg/day for 90 days by oral gavage³. The results of this study demonstrate an absence of adverse effects in rats, with an NOAEL of at least 1,000 mg/kg/day for Phase 2[®] administration by oral gavage. These dose levels support human oral intakes of up to approximately 10,000 mg Phase 2[®] per person per day (*i.e.*, 142.9 mg/kg/day assuming a 70 kg human). The highest dose given to rats in this study (1,000 mg/kg/day) would be equivalent to approximately 70 g/day in a 70-kg person, approximately 7-fold greater than the maximum recommended daily intake of 10 g/day from all food and supplement use applications.

The Experts also noted supporting evidence of safety from a series of toxicological studies performed by the distributor of BLOCKAL, a dietary supplement containing approximately 56% Phase 2[®] extract⁴. The experimental animal studies have shown that exposure to oral doses of approximately 1000 milligrams of Phase 2[®] per kilogram of body weight per day was not associated with any adverse health effects. Phase 2[®] has also exhibited no evidence of hemagglutinating or trypsin inhibition activity.

Supportive evidence of safety was also presented in clinical studies, conducted in both the United States and Europe, designed to primarily examine the effects of Phase 2[®] or dietary supplements containing Phase 2[®] (Blockal, TheraSlim™, Starch Away™) on glucose response and body weight loss. However, at least two studies included tests for hematology, clinical chemistry, and/or urinalysis. During these studies, Phase 2[®] was administered to healthy subjects with meals at levels ranging from 500 to 3000 mg per day for periods from 30 days to 24 weeks. No effects of toxicological concern were observed in any of these studies.

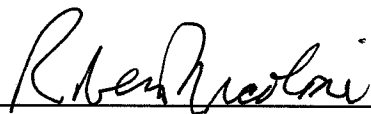
² Chokshi, D. 2007. Subchronic oral toxicity of a standardized white kidney bean (*Phaseolus vulgaris*) extract in rats. *Food Chem. Tox* 45:32-40.

³ Harikumar, KB, Jesil, AM, Sabu, MC, Kuttan, R. 2005. A preliminary assessment of the acute and subchronic toxicity profile of Phase 2: An α -amylase inhibitor. *Int J Toxicol* 24:95-102.

⁴ Chokshi, D. 2006. Toxicity studies of Blockal, a dietary supplement containing Phase 2 Starch Neutralizer™ (Phase 2[®]), a standardized extract of the common white kidney bean (*Phaseolus vulgaris*). *Int J Tox* 25:361-371.

In addition, the Experts noted results of regularly conducted tests on production lots of Phase 2[®] for *in vitro* activity of two anti-nutritive substances that have been identified in crude extracts of kidney beans, hemagglutinins (lectins) and trypsin inhibitors. The results of 10 lots tested revealed that hemagglutinin activity in Phase 2[®] was 50 to 1600 times lower than that of soybean lectins. Trypsin inhibitor activity (TIA) was 3 to 4 times lower than that of defatted soybean flour. Given a 12:1 ratio in concentrating the aqueous Phase 2[®] extract from its source, and assuming all other trace contaminants present in the beans were concentrated into the Phase 2[®] fraction, then consuming 10 grams of Phase 2[®] would entail exposure to these microcontaminants equal to consumption of approximately 120 grams of dry beans.

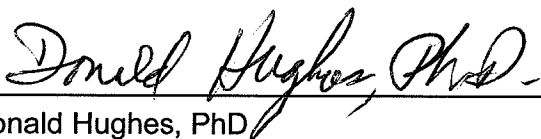
After a critical independent evaluation of the available safety and clinical information, the undersigned Experts conferred and concluded that Phase 2[®] is Generally Recognized as Safe (GRAS) by scientific procedures at the proposed upper limit of aggregate intake of 10 g of Phase 2[®] per day from dietary supplement and food use applications for which no defined standard of identity exists.



Robert Nicolosi, PhD
Director, Department of Health and Clinical Science
University of Massachusetts, Lowell
3 Solomon Way, Suite 4
Lowell, MA 01854-5125

2/20/07

Date



Donald Hughes, PhD
12154 Scoutmaster Drive
Cincinnati, OH 45241

2/24/07

Date



David Bechtel, PhD
Vice President and Senior Scientific Consultant
CANTOX U.S. Inc.
1011 US Highway 22, Suite 200
Bridgewater, NJ 08807

2-15-07

Date