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1001 G STREET, N. W.
SUITE 500 WEST
WASHINGTON, D.C. 20001
TEL. 202.434.4100
FAX 202.434.4646
WWW.KHLAW.COM

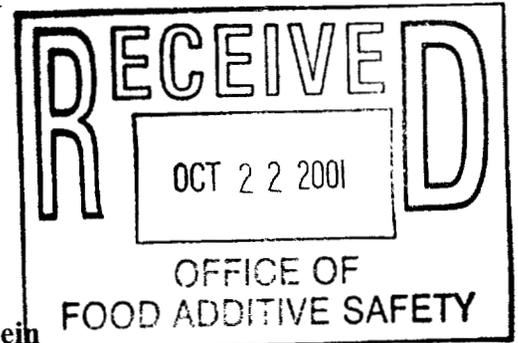
WRITER'S DIRECT ACCESS

John S. Eldred
(202) 434-4176
eldred@khlaw.com

October 19, 2001

VIA HAND DELIVERY

Linda S. Kahl, Ph.D.
Office of Premarket Approval
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, S.W. (HFS-206)
Washington, D.C. 20204



Re: GRAS Notification for Coagulated Potato Protein

Dear Dr. Kahl:

On behalf of our client, Avebe b.a., pursuant to the Food and Drug Administration's April 17, 1997 proposed rule, we are submitting (in triplicate) the enclosed notification regarding the generally recognized as safe (GRAS) status of coagulated potato protein for use in fat and water binding, emulsifying and foaming in various foods. If you have any questions regarding the notification, please contact me.

Respectfully submitted,

A large, empty rectangular box outlined in red, intended for a signature.

John S. Eldred

Enclosures

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Before the
FOOD AND DRUG ADMINISTRATION
Department of Health and Human Services
Washington, D.C.

GRAS NOTIFICATION

Name of Notifier: AVEBE b.a.

Post Office Address: All communications on this matter are to be sent in care of Counsel for the Notifier, John S. Eldred, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001.

Telephone: (202) 434-4176.

Name of Substance and Intended Use: Coagulated potato protein, in hydrolyzed and unhydrolyzed form, for use in fat and water binding, emulsifying and foaming in various foods.

Dated: October 19, 2001

John S. Eldred
Counsel for AVEBE b.a.

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1. Claim of GRAS Status

(i) Name and Address of Notifier:

AVEBE b.a.
Prins Hendrikplein 20
9641 GK Veendam
The Netherlands

All communications on this matter are to be sent in care of Counsel for the Notifier, John S. Eldred, Keller and Heckman LLP, 1001 G Street, N.W., Suite 500 West, Washington, D.C. 20001.
Telephone: (202) 434-4176.

(ii) Common or usual name of the notified substance:

The common or usual names of the forms of potato protein that are the subject of this notification are coagulated potato protein, hydrolyzed potato protein and clarified hydrolyzed potato protein. The substance consists of potato protein isolated by heat coagulation from conventional potatoes which is optionally enzymatically hydrolyzed. The hydrolyzed protein is optionally clarified.

(iii) Applicable conditions of use:

The potato protein, in both its hydrolyzed and unhydrolyzed forms, is intended for use for a variety of functional effects associated with proteins, e.g., as a water binder in meat and sausage, as a foaming aid in confectionary, bakery and dairy products, and as an emulsifier in spreads, sauces, desserts and dressings.

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(iv) Basis for GRAS determination

The described use of coagulated potato protein and hydrolyzed coagulated potato protein has been shown to be generally recognized as safe (GRAS) on the basis of scientific procedures, in accordance with 21 C.F.R. § 170.30, as discussed more fully in the accompanying summary of the basis for the GRAS determination.

(v) Statement of availability of data

The data and information that are the basis for the GRAS determination are available for the Food and Drug Administration's review and copying or will be sent to FDA upon request.

* * *

The foregoing and attached information considered, it is respectfully submitted that the use of coagulated potato protein and hydrolyzed potato protein for use in various foods as a binder, foamer and emulsifier, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because it is generally recognized as safe.

Respectfully submitted,

AVEBE b.a.

By: _____
John S. Eldred
Keller and Heckman LLP

COUNSEL FOR THE NOTIFIER

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2. Identity of the Notified Substance

The notified substance is potato protein isolated from conventional potatoes after grinding and separation of starch and fibers by a thermal coagulation process. This process yields coagulated protein dispersed in water, which is further washed and refined to yield a food-grade coagulated potato protein (CPP). The CPP may be sold as such for use in food or may be enzymatically hydrolyzed using a safe and suitable enzyme to obtain hydrolyzed potato protein (HPP). The HPP may be sold as such for use in food or may be further refined to isolate a fully soluble protein fraction, hydrolyzed clarified protein (HCP). CPP, HPP and HCP have different physical properties but are virtually identical toxicologically; CPP is the parent protein; HPP is the enzymatic hydrolysate; and HCP is the water soluble fraction of HPP.

<i>Chemical Names:</i>	Coagulated Potato Protein (CPP) and Potato Protein Hydrolysates (HPP and HCP)
<i>CAS Registry:</i>	None. The product is a natural protein
<i>Molecular and structural formula:</i>	Similar to cooked potato protein.
<i>Quantitative composition:</i>	Complies with purity specifications set forth below.
<i>Method of Manufacture:</i>	Described below.

The manufacturing process is summarized in Chart I in the Appendix. The protein is produced in the same plant as food-grade potato starch under GMP conditions.

The production of CPP starts with the thorough washing of the potatoes in water (step 1). Then they are ground in rasps (2) which break up the potatoes into a potato mass. In this stage sulfite is added to repress oxidative browning. The mass is sieved (3) to remove fibers after which a starch milk is obtained. The starch milk is fed to hydrocyclones (4) to separate the ground starch from the "fruit juice", which contains dissolved protein. (Alternatively, starch and fibers may be separated from the fruit juice together, depending on the specific production plant.) The "fruit juice" is then adjusted to a suitable pH (5) and steam is injected to raise the temperature to > 80°C (6). The protein precipitate is removed by means of centrifugal force using a decanter (7). Optionally, the protein can be dried (8).

The coagulated protein is further processed according to the scheme (Chart II in the Appendix). The protein is dispersed in dilute food-grade mineral acid (1), decanted and washed with water (2) optionally followed by pH adjustment and/or drying (3) to yield food-grade CPP. The cleaned protein is dispersed in water (4) and the pH is adjusted (5) to a value appropriate for the enzyme to be used. A food-grade protease is added (6). After a certain amount of time, the

reaction is stopped by heating the mixture to $> 85^{\circ}\text{C}$ to inactivate the protease (7). The partially solubilized protein is isolated by drying the mixture (8) to yield hydrolyzed potato protein (HPP).

Alternatively, the mixture may be separated using a decanter and separator (9) into a fully soluble, hydrolyzed, clarified potato protein (HCP) and a partially soluble fraction, both of which are dried. Both HPP and HCP as well as CPP are included in this notification.

The process of manufacturing CPP does not change the primary chemical structure of the protein and is comparable to the denaturation of potato protein during boiling of potatoes. Therefore, CPP is essentially equivalent to the protein in boiled potatoes. In the production of HPP and HCP, proteases in an aqueous medium are used to partially hydrolyze the protein. This improves the properties of potato protein for use in a number of food systems. In the human digestive tract, the potato protein in common potatoes is also subjected to hydrolysis by proteases in an aqueous medium. Thus the hydrolyzed potato protein products, HPP and HCP, are comparable to partially pre-digested potato protein from eating ordinary cooked potatoes.

Characteristic properties – CPP is potato protein that has been obtained from ordinary potatoes, washed and processed by heat treatment. It has the characteristics of cooked protein and is sold as a dry powder. HPP and HCP are products obtained from the partial enzymatic hydrolysis of CPP. They are proteins also, but of lesser average molecular weight and have physical properties suitable for incorporation in a wider variety of foodstuffs. For example, HCP is completely water soluble.

Food-Grade Specifications – The specifications for food-grade CPP, HCP and HPP are given in Table 1. These specifications include the protein, dry matter and ash content and set maximum levels of certain components requiring control from a toxicological point of view, i.e., glycoalkaloids and lysinoalanine. (The safety of these components is discussed in Section 4 (i)). These three products are all closely related, and they all comply with the same specifications. In the process of enzymatically hydrolyzing CPP, smaller fragments of protein (from a few to about 20 amino acids) are liberated which dissolve. The complete mixture is HPP, whereas the isolated soluble fragments are HCP. These three products differ only in the degree of hydrolysis and accordingly in the average molecular weight of the proteins.

Table 1		
Specification of Food-grade CPP, HPP and HCP		
Element	Relative Amount in Product as sold	Amount in 100 g Product as sold
Water	< 200 mg/g	< 20 g
Dry matter	> 800 mg/g	> 80 g
Protein (N x 6.25)	> 600 mg/g dry matter	(>0.6 x 80) > 48 g
Ash	< 400 mg/g dry matter	(<0.4 x 80) < 32 g
Glycoalkaloids	< 150 ppm	< 15 mg
Total lysinoalanine	< 500 ppm	< 50 mg
Free lysinoalanine	< 10 ppm	< 1 mg

Table 2 contains an analysis of the inorganic elements in the product. HCP I and HCP II are different batch versions of HCP. In the process of hydrolyzing CPP to make HCP, the pH tends to drop when the enzymes hydrolyze proteins. Alkali is added to maintain the pH constant. The ash value for CPP is in the range of 4-5% while the ash value for the hydrolysates is much higher. This increase in ash content reflects the addition of alkali and includes the weight of the metallic elements and the anion corresponding to the acid used for pH adjustment, which is the major anion in the hydrolysate. As Table 2 indicates the levels of heavy metals are very low. The specification for ash in Table 1 (< 40 %) is much higher than the typical HCP or HPP hydrolysate and covers potential outliers. The amount of sulfite is drastically reduced in going from CPP to the hydrolysates due primarily to volatilization of SO₂ and also retention of sulfite in the non-soluble fraction.¹

¹ Avebe will advise its customers of the level of sulfites in CPP and HPP and HCP so that the customers can comply with FDA's sulfite ingredient declaration requirements when sulfite levels in the finished food are 10 ppm or greater. Avebe's potato protein products are not intended for use in any of the foods in which the use of sulfites is prohibited pursuant to the GRAS regulations for sulfiting agents, e.g., 21 C.F.R. § 182.3862, which prohibits the use of sulfur dioxide in meats; in food recognized as a source of vitamin B1; on fruits and vegetables intended to be served raw to consumers or sold raw to consumers, or to be presented to consumers as fresh. With regard to the use of potato protein with residual sulfite in meat products, while USDA prohibits the direct addition of sulfites to meat, that Agency's policy (embodied in Food Safety and Inspection Service Policy Memo 094B) is to allow the presence of sulfites in ingredients which are themselves used in formulating meat and poultry products, subject to the same 10 ppm sulfite labeling requirement as is imposed by FDA.

Table 2 Analysis of the Inorganic Elements in the Product			
Element	CPP	HCP 1	HCP II
water	9.5 %	4.0 %	3.3 %
dry weight	90.5 %	96.0 %	96.7 %
-----	-----	-----	-----
protein (dry)	89.0 %	66.9 %	70.6 %
ash	4.8 %	21.8 %	18.5 %
sodium	34 ppm	5.4 %	2.6 %
potassium	37 ppm	300 ppm	n.d.
phosphorous	0.15 %	5.2 %	4.5 %
arsenic	0.02 ppm	0.1 ppm	0.04 ppm
cadmium	0.040 ppm	0.035 ppm	0.045 ppm
copper	35 ppm	16 ppm	19 ppm
mercury	< 5 ppb	< 5 ppb	< 5 ppb
lead	< 50 ppb	< 50 ppb	< 50 ppb
zinc	2.5 ppm	1.5 ppm	2.0 ppm
sulfite	324 ppm	< 5 ppm	< 5 ppm

Microbiological Quality – Analytical results of typical microbiological indicators are listed in Table 3. These data show that the products are well within current safety limits for food ingredients and that the control points in the process are adequate. The heat treatment of PP which forces coagulation is also a critical control point for microbiological quality.

Table 3 Typical Microbiological Analyses of Products (cfu/g)			
Species	CPP	HCP I	HCP II
Total aerobic count	5.5×10^2	$< 10^2$	6.4×10^3
<i>Enterobacteriaceae</i>	< 10	< 10	< 10
Yeast	270	90	30
Moulds	< 10	< 10	< 10
Sulfite reducing	$< 10^2$	n.d.	n.d.

Enzymes – A food-grade protease that is properly considered to be GRAS is used in the production of the HCP and HPP hydrolysates.

Protein Quality – Table 4 lists the amino acid composition of CPP and HCP. These analyses were carried out according to ISO 9001 procedures. (See TNO Nutrition in references.) The amino acid composition of HPP is the same as CPP. The main difference in the amino acid composition between HCP and HPP/ CPP is the somewhat lower cystine and tryptophan content. This is the result of the tendency of the hydrophobic amino acids and cystine to stay in the insoluble fraction. Nutritional analyses have been conducted on CPP and HCP, in particular: protein content, ash, and amino acid composition. All the information leads to the conclusion that potato protein has a higher nutritional value than soy protein and is close to that of casein. This is mainly the result of the high lysine content in combination with good digestibility.

Amino Acid	CPP (mg/g protein)	HCP I (mg/g protein)	HCP II (mg/g protein)
Alanine	53	60	60
Arginine	50	46.5	48
Aspartic acid	124	131	128
Cystine	15.6	8.9	9.6
Glutamic Acid	115	124	125
Glycine	51	51	51
Histidine	22.4	20.4	22
Isoleucine	61	52	54
Leucine	107	99	101
Lysine	79	75	76
Methionone	22.9	20.8	21.6
Phenylalanine	63	58	59
Proline	48	50	55
Serine	54	52	55
Threonine	61	61	61
Tryptophan	14.8	5.1	8.4
Tyrosine	56	46	51
Valine	65	61	65

The amino acids were measured by accepted ISO methods (TNO Nutrition, Methods for analysis of amino acids: DBGT/AZA/001; DBGT/AZA/002; DBGT/AZA/003).

3. Information on Self-Limiting Levels of Use

The potato protein products will be used as food ingredients by the food processing industry in a variety of applications, for example certain bakery products, salad dressings, confections, meat products and gluten-free foods. These products will not be directly supplied to the consumer. The products offer, in addition to their favorable nutritional properties, a range of functionalities such as water binding, emulsifying or foaming. The potato protein products will replace other protein products, either animal or vegetable proteins, that are currently being used. Since the product is essentially a food, its use is limited only in the sense that there is a finite market for such products.

4. Summary of Basis for GRAS Determination

(i) Safety of CPP, HPP and HCP

As indicated above, general recognition of safety is based primarily on scientific procedures, in keeping with 21 C.F.R. § 170.30(b), by demonstrating—via analytical data—that these products are, in all important respects, equivalent to the proteins in conventional potatoes. Furthermore, there is no significant difference in the safety of CPP, HPP, and HCP. CPP is essentially cooked potato protein. As indicated above, HPP and HCP are enzymatic hydrolysis products of CPP, by a process virtually identical to that which occurs during human digestion. Because the amino acids come from protein, with the full complement of amino acids, there is no unusual addition of any individual amino acid to produce an amino acid imbalance and cause a safety concern.

Similarity of ordinary cooked potatoes – With the possible exception of lysinoalanine, which is considered separately, each of the proposed potato protein products contains only components that are present in approximately the same quantity in ordinary cooked potatoes or in cooked, digested potatoes. (See discussion in this Section and Tables 4 and 5.) Ordinary potatoes are therefore the traditional counterpart to these potato protein products and provide a baseline for the toxicological assessment. Because of washing and the dispersion of the protein in water at several points in the process, the glycoalkaloid level is controlled at a substantially lower level than the glycoalkaloid level in the whole potato based on protein content. Water soluble impurities and heavy metal levels are kept low by the same process. The level of toxicants is therefore reduced compared to the traditional counterpart.

Potatoes are one of the five most important world crops. They are consumed without detrimental effects by all groups of the world's population. The consumption of potatoes in Europe is on the average of 200-250 g per day, while the United States average consumption is significantly lower, at 61 g/day (*USDA Data Tables, 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey, Table 9.2, Table set 10*). Potatoes have been consumed in amounts up to several kilograms per day for long periods without ill effect. The content of PP in potatoes is approximately 2% corresponding to a daily intake of (61 x 0.02 = 1.2 g).

The anticipated level of PP in various processed food products is between 0.1 and 3.0%. Estimating 129 g intake of PP-containing processed food daily, the amount of added PP ingested would be expected to be approximately 1.9 g. (See Consumption Estimate below.) This would more than double the daily intake of PP from potatoes and result in a maximum cumulative PP intake of approximately 1.2 + 1.9 = 3.1 g/day. This PP protein will, for the most part, substitute or replace competitive soy or wheat-based protein products. Since the average protein intake for all individuals is 75.1 g/day, this increase in PP would not significantly change the composition of an individual's protein profile (*USDA Data Tables, 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey, Table 1*).

Nutritional Quality of CPP and Hydrolysates – A typical composition of potato protein isolated by thermal coagulation is given in Table 4 (AVEBE data) and this is compared with potato, egg and beef protein in Table 5 (Woolfe, 1987). The amino acid composition of CPP is comparable to that for the protein in cooked potato. Potato protein is remarkably close to animal protein as indicated in Table 5. The nutritional value of CPP is excellent, mainly due to its content of essential amino acids, including lysine and the sulfur-containing amino acids.

Table 5
Essential Amino Acid Composition of Potato and Comparison with Other Proteins

Amino Acid	Protein content (mg/g crude protein) in:			Required protein (mg/g protein) by adult male
	Potato	Egg	Beef	
Histidine	20	22	34	16
Isoleucine	39	54	48	13
Leucine	59	86	81	19
Lysine	60	70	89	16
Methionine + Cystine	15+15 =30	57	40	17
Phenylalanine + Tyrosine	43+35 =78	93	80	19
Threonine	39	47	46	9
Tryptophan	14	17	12	8
Valine	51	66	50	13

Most of the essential amino acids are present in larger relative amounts in CPP than in fresh potato. This is caused by the relative abundance of aspartic and glutamic acids in non-protein nitrogen and the relatively low content of some essential amino acids in non-protein nitrogen, which is the fraction removed from the isolated potato protein.

Total Glycoalkaloids (TGA) – The common potato produces two major glycoalkaloids (GA)- α -chaconine and α -solanine, often referred to collectively as “TGA” or “solanine”. The highest concentrations of TGA are present in the peel and in the tissue layer just below it (Nordic Working Group, 1990). The levels in consumer varieties of potatoes range from 20-150 ppm TGA. The glycoalkaloids present in potatoes are recognized as toxic substances. The typical 20-150 ppm levels in potatoes (average = 80 ppm) are usually not harmful to humans. But infrequently, in green potatoes, exposed to sunlight, “solanine” levels have gotten large enough to poison animals and humans. Values of approximately 400 ppm “solanine” have been obtained for potatoes implicated in human fatalities. An average intake of TGA (80 ppm) from potatoes in the U.S. is $61\text{g} \times 80\text{ mg/kg} = 4.9\text{ mg/day} = 0.08\text{ mg/kg.bw/day}$. A European NOEL has been established at 200 ppm TGA, which corresponds (assuming 300 g of potatoes daily in Western Europe) to $300 \times 200\text{ mg/kg} = 60\text{ mg/day}$ or to approximately 1.0 mg/kg.bw/day (Nordic

Working Group, 1990). Thus, the margin of safety for TGA in conventional potatoes in the U.S. is $1.0/0.08 = 12.5$. Most consumers will be exposed to much smaller amounts due to the loss from peeling.

“Solanine” Intake from PP Products – The maximum intake of potato protein in PP products, as shown below, is estimated at 1.9 g/day (meaning CPP, HPP, and HCP) and about 1.2 g/day in potatoes themselves. The level of total glycoalkaloids (TGA) is specified to be less than 150 ppm in the product. This gives a daily TGA content in PP-containing processed food of < 0.28 mg ($1.9 \text{ g/day} \times 0.15 \text{ mg/g} = 0.28 \text{ mg/day}$). This compares to the daily U.S. intake of 4.9 mg/day from potatoes. The increment of TGA from anticipated PP products increases the daily TGA intake by $0.28/(4.9 + 0.28) \times 100$ or 5.4 % and slightly reduces the safety margin from 12.5 to 60/5.18 or to 11.6. This is a barely detectable change and we conclude that the use of the product will not increase the risk from solanine in potatoes significantly.

Occurrence of Lysinoalanine – Treatment of protein by heat or by alkali during food processing has long been known to lead to structural changes and to the formation of unusual cross-links. When the protein is hydrolyzed back to the amino acids, sometimes unnatural amino acids are found. Bohak *et al.* reported that treatment of proteins at pH 12.2 and 25°C or pH >8 and 100°C leads to the formation of cross links in the protein, which after hydrolysis, produces lysinoalanine (LAL) (Bohak, 1964). Lysinoalanine is also obtained after alkali treatment of lysozyme, papain, chymotrypsin, bovine plasma albumin, but not pepsin or pepsinogen.

It was later reported that LAL was present in many processed proteinaceous foods that had simply been heated or cooked. These include heated milk, simulated cheese, cooked egg whites, cooked chicken, cooked corn products, acid casein, hydrolyzed vegetable protein, and whipping agent (Sternberg *et al.*, 1975). It seems generally true that heating protein can be expected to produce LAL in protein-containing foods. These findings indicate that LAL, at least in protein bound form, is a normal and ubiquitous constituent of the human diet (Sternberg *et al.*, 1975).

In the course of the manufacturing process for PP, the proteins are removed from the “potato fruit juice” by heat coagulation. This involves an adjustment of pH usually to 4.8-8.0 and the injection of steam to a temperature of > 80°C. This heat treatment results in the denaturation and precipitation of the proteins and possibly the formation of lysinoalanine cross-links. Other unusual amino acids, e.g., orthinoalanine and D-serine, may, like lysinoalanine, be formed at high pH and/or temperature. However, for various reasons these are expected to be present at much lower levels than LAL (Feron *et al.*, 1977, Ziegler *et al.*, 1967 and Beek van *et al.*, 1976).

Toxicity of Lysinoalanine – Lysinoalanine has been implicated as a renal toxin in rats (Woodard and Short, 1973). Woodard *et al.* reported a LOAEL in rats consuming 0.025% LAL in the diet or 250 ppm $\times 0.05 = 12.5 \text{ mg/kg.bw/day}$ (Woodard *et al.*, 1975; Woodard and Alvarez, 1967). The renal lesions were characterized by cytomegalic alterations of the straight portion, pars recta, of the renal tubule. According to De Groot *et al.* (1976), renal changes were observed

in rats fed 100 ppm synthetic lysinoalanine for 90-days but not at 10 ppm or 30 ppm. This would give a NOEL of 30 ppm or $(30 \text{ ppm} \times 0.05) = 1.5 \text{ mg/kg.bw/day}$. Using a safety factor of 1000, as traditionally done by FDA with 90-day studies, would give an ADI of $1.5 \mu\text{g/kg.bw/day}$ for the renal cytomegaly for free lysinoalanine. Clinical signs of renal failure do not occur in rats until dietary levels of 10,000 ppm are fed. The relatively low level required to induce cytomegalia and the high level required to provoke functional disturbance in rats suggests that cytomegalia may be of little clinical significance. Reyniers *et al.* (1974) have suggested that LAL-induced megalocyte transformation could represent a renal homeostatic mechanism rather than a degenerative phenomenon.

In a long term study with free lysinoalanine in rats, Feron *et al.* (1978) fed diets containing 0 or 200 ppm synthetic lysinoalanine. Nephrocytomegaly became increasingly severe with exposure time from 4 to 52 weeks; however, there were no signs of proliferative or neoplastic changes in any of the kidneys.

In contrast to the results with free LAL, no renal cytomegalic changes occurred when rats were fed diets containing alkali-treated proteins at much higher levels (De Groot *et al.*, 1976). The proteins used in these studies were always washed to remove any water soluble degradation products, including free LAL. These studies showed that the ability to induce cytomegaly is a property of the free compound and that little or no activity is exerted if the compound remains an integral part of the protein molecule. The absence of adverse renal effects when feeding protein-bound LAL is thought to be due in part to poor absorption of the LAL-protein from the intestinal tract. However, evidence was obtained that if the LAL is bound to relatively small molecular weight protein fragments, < 5000 , the cytomegalic tendency is retained although reduced in potency (De Groot *et al.*, 1976). LAL was tested in a variety of other animals species. The absence of renal effects in quail, mice, hamsters, rabbits, dogs and monkeys fed a high level of the free compound indicate that the renal cytomegalia induced by free LAL may be a phenomenon unique to the rat (De Groot *et al.*, 1976).

Specification of LAL for PP – A 1979 FASEB Panel (SCOGS) Report considered the LAL toxicity question in its evaluation of the “Health Aspects of Soy Protein Isolates as Food Ingredients”. They concluded that the levels of lysinoalanine in currently used, food-grade soy protein isolates posed no hazard to consumers. Nonetheless, they recommended that lysinoalanine levels be restricted in the specifications for food-grade soy protein products to avoid possible future problems. The levels of use for potato protein products would be similar to soy protein products and we therefore follow the FASEB approach by including a specification limiting the amount of lysinoalanine in the product. The specifications for total lysinoalanine (LAL), bound and unbound, in Table 1 are $<500 \text{ mg/kg}$ ($<10 \text{ ppm}$ free and $<500 \text{ ppm}$ total). If we assume a total daily intake of 1.9 g/day PP, the maximum estimated daily intake (EDI) of the most potent free lysinoalanine is $1.9 \text{ g/day} \times 10 \mu\text{g/g} = 19 \mu\text{g/day}$ or $19 \mu\text{g/day} / 60 \text{ kg.bw} = 0.32 \mu\text{g/kg.bw/day}$. The specification of total LAL is based on the observation that the free LAL is at least 60 times more potent than bound LAL. The ADI for free LAL is $1.5 \mu\text{g/kg/bw/day}$ or at least 5 times the EDI.

Allergenicity – Potatoes have long been regarded as a safe and non-allergenic food, despite rare allergic responses to inhalation of potato dust and skin contact with potato peelings. Raw potatoes are known to elicit infrequent allergic responses, primarily in people peeling potatoes who are allergic to either birch pollen or latex (Nater *et al.*, 1967; Wahl *et al.*, 1990). This allergic cross-reactivity is induced because of structural similarities between birch pollen and latex to specific undenatured potato protein(s). Cooked potatoes, comprising denatured proteins, however, are usually well tolerated in such individuals (Nater *et al.*, 1967, Hannukslea and Lahti, 1977). Much evidence indicates that denaturation of potato protein leads to a decrease in any potential food allergy due to potatoes (Hefle *et al.*, 1996). The potential allergenicity of CPP and its hydrolysates should be the same or less than that of ordinary cooked potatoes.

It is helpful to place potato allergy in context with other food allergies. Sampson and McCaskill (1985) tested food hypersensitivity in 113 severe atopic subjects, who ranged in age from 4 months to 24.5 years. Six foods: eggs, peanuts, milk, soy, wheat and fish accounted for more than 85% of the positive reactions to food allergens in these subjects. However many foods contain other low grade allergens, to which a few people are allergic. Potato, beef, pork and chicken each accounted for approximately 2%. In pinprick tests applied to these 113 subjects, positive reactions to various foods occurred in the following numbers: egg (55), peanut (49), milk (26), wheat (15), soy (24), fish (29), chicken (19), pork (32), beef (18), potato (7), pea (19), shrimp (18), rice (10), tomato (5), green bean (7), corn (7), chocolate (4), rye (8), oats (7) and strawberry (1). From these data it is clear that potato allergy is not common and occurs with approximately the same frequency as allergy to many common foods that are not considered to pose allergenicity concerns.

A recent Finnish study (Seppälä *et al.*, 1998), suggests that atopic children may be sensitive to potatoes as food, i.e., cooked potato, because of a specific protein. These authors indicate that patatin, the main storage protein in potatoes, binds IgE from the sera of atopic children with a positive pin prick test response to raw potatoes. In addition, purified undenatured patatin caused positive skin prick reactions in children suspected of having allergy from potatoes. Finnish authors conclude that further studies are needed to assess the clinical importance of potatoes, and especially patatin, as a food allergen (Seppälä *et al.*, 1998).

In view of the large quantity of potatoes eaten for centuries without the occurrence of any large scale potato allergy, and because of the equivalence of PP to cooked potato, there is little reason for concern about the allergenicity of PP.

(ii) Intake of PP from Notified Use

The potato protein products will be used as food ingredients by the food processing industry in a variety of applications, for example bakery products and salad dressings, confections and gluten-free foods. These products will not be directly supplied to the consumer. The products offer, in addition to their favorable nutritional properties, a range of functionalities

such as water binding or foaming. The potato protein products will replace other protein products, either animal or vegetable proteins, that are currently being used.

The anticipated level of PP in various processed food products is between 0.1 and 3.0% in the final product. Based on USDA frequency data and USDA mean portion size, our estimate for the mean consumption (males/females 2-65+years) of the baked goods in which PP could be used is 83 g/day; dairy products- 10 g/day; salad dressing- 8 g/day; confections- 7 g/day; and for processed meat products, we estimate 21 g. This yields a total EDI of 129 g.

Consumption Estimate		
From 1994-1996 USDA Continuing Survey of Food Intake by Individuals and 1994-96 Diet and Health Knowledge Survey, From Table Set 10		
Food Category	Mean Intake (grams/day)	Notes
Baked Goods	83	See explanation in text
Dairy	10	Aerated desserts
Salad dressing	8	Fat and oil based only
Confections	7	Includes soft and hard candies and sweets.
Processed Meat Products	21	Includes; frankfurters, sausages, luncheon meats
Total	129 g	Estimated EDI

The consumption estimates were derived from USDA food consumption surveys. Baked goods are not listed, *per se*, in the USDA data, but "grain products" are. The USDA Tables list a total consumption of 302 grams/day for grain products. This category includes, yeast breads and rolls (50 g), ready to eat cereals, rice and pasta (74 g), quick breads, pancakes and toast (19 g), cakes, cookies, pastries and pies (38 g), crackers, popcorn, pretzels and corn chips (12 g), and mixtures, mainly grain (109 g). To estimate the consumption of baked goods we summed the intakes of the baked goods in which PP is expected to be used, e.g. cakes, cookies, pastries and pies, crackers, popcorn, pretzels, and corn chips and 30% of the mixtures, to yield $38 + 12 + 33 = 83$ g.

The anticipated level of PP in various processed food products will range between 0.1% and 3.0%. We assume that the average concentration of PP in food will be conservatively half the high end of this range or 1.5%. Assuming a total 129 g/d intake of PP-containing processed food daily, and an average PP concentration of 1.5%, the amount of added PP ingested would be approximately 1.9 g ($1.5\% \times 129$ g).

This PP protein will, for the most part, substitute or replace competitive soy or wheat-based protein products. Since the average protein intake for all individuals is 75.1 g/day, this

intake of PP would not significantly change the composition of an individual's protein profile (*USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey, Table 1*).

(iii) Cumulative Intake of PP

The average intake of potatoes in the United States (all individuals) is 61 grams. Assuming a PP content of approximately 2%, the amount of PP already consumed in potatoes is approximately 1.2 g/day (2% x 61g) (*USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey, Table 1*). Thus, the consumption of CPP products, if ingested at the estimated rate, would increase the daily amount of PP consumed from approximately 1.2 g to (1.2 + 1.9) or 3.1 g.

(iv) Information Unfavorable to the GRAS Determination

The notifier is not aware of any reports of investigations or other information that might appear to be inconsistent with the GRAS determination.

(v) Basis for Concluding that the Notified Use of PP Is GRAS

General recognition of safety under scientific procedures requires two findings (1) that a substance is generally recognized as safe on the basis of a scientific evaluation of toxicity and level of use, and (2) that the scientific information on which this assessment is based is generally available. Analytical data demonstrate that PP (including CPP, HPP and HCP) has been shown to be compositionally identical, in all significant respects, to cooked potato protein and hence toxicologically equivalent to potato protein, which is consumed daily as a major source of food by hundreds of millions of people and has been for hundreds of years. Regarding the contaminant LAL, published toxicological studies demonstrate that LAL is safe at the use levels. Levels of TGA in CPP, HCP and HPP are safe. The amount of TGA consumed in PP products would amount to but a small fraction—approximately 5%—of TGA consumed now from potatoes in the U.S. The intake of the notified product will be approximately 1.9 g/day, and will contribute to the total intake of approximately 75 g/day protein. As discussed above, the chemical structure, physical properties and toxicity of PP are similar to those of other proteins and are well established in the scientific community.

* * *

The foregoing and attached information considered, it is respectfully submitted that, under the conditions of intended use, coagulated potato protein, in its hydrolyzed and unhydrolyzed form, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because it is generally recognized as safe.

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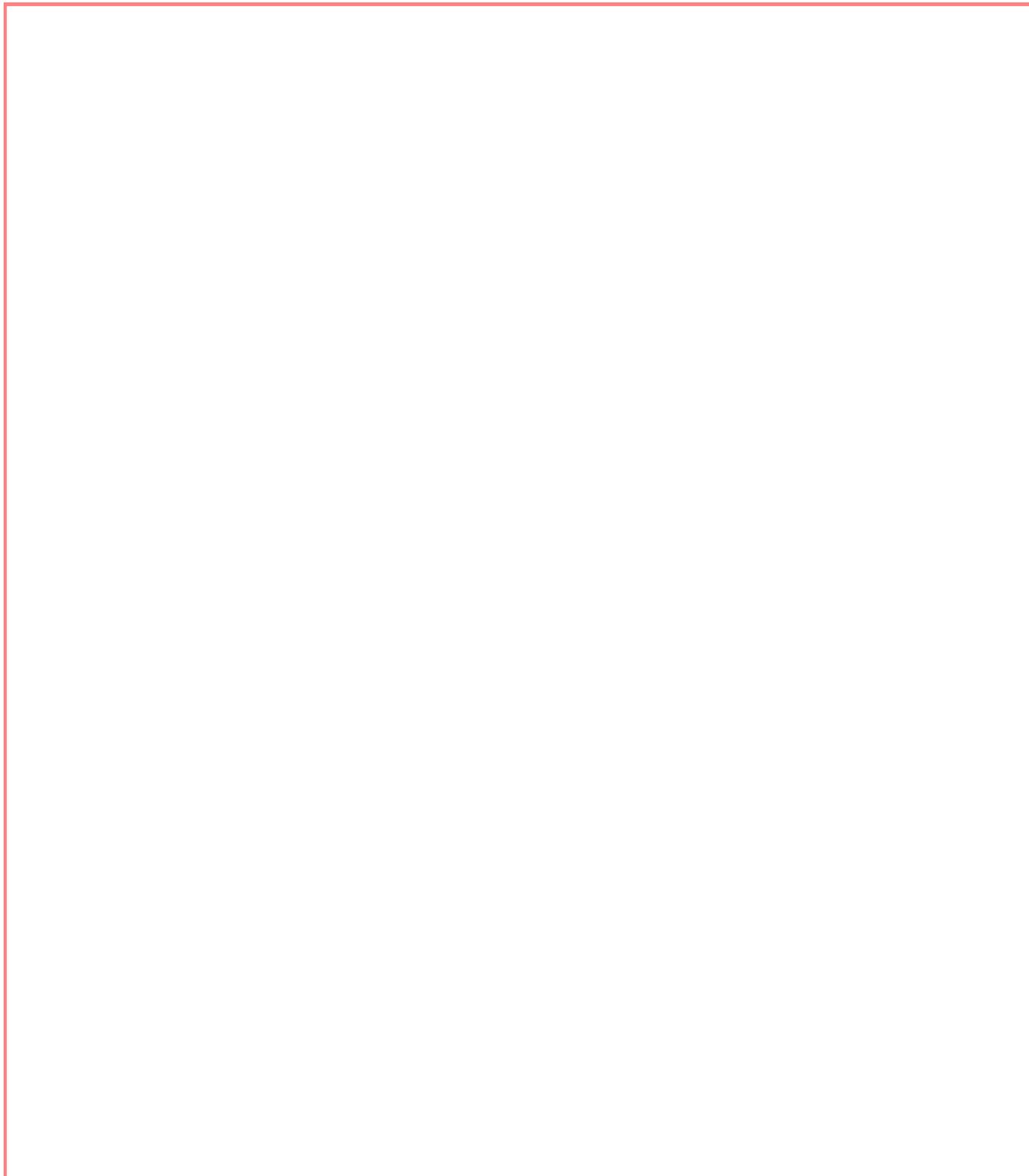
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APPENDIX

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Description of the production process of potato protein and hydrolysates thereof

Coagulated potato protein



Potato protein products for food applications

SUBMISSION END

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