October 25, 2000

HAND DELIVERY

Document Processing Desk (AMEND)
Office of Pesticide Programs, BPPD – H7504C
U.S. Environmental Protection Agency
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202-4501

BRANCH CHIEF: Phil Hutton
ATTENTION: Michael Mendelsohn

SUBJECT: **Updated safety assessment in support of the pesticide petition for a time-limited exemption from the requirement of a tolerance for the plant-pesticide *Bacillus thuringiensis* subsp. *tolworthi* Cry9C and the genetic material necessary for the production of this protein in or on all raw plant agricultural commodities.**

RE: EPA REGISTRATION NUMBER 264-669

Dear Mr. Hutton,

Please find enclosed an addendum to the Aventis CropScience USA, LP (Aventis) original food tolerance exemption petition for Cry9C corn. The addendum is in support of a time-limited exemption from the requirement of a food tolerance for the plant-pesticide *Bacillus thuringiensis* subsp. *tolworthi* Cry9C and the genetic material necessary for the production of this protein in or on all raw plant agricultural commodities. This document was generated with input from the Grocery Manufacturers of America, the National Food Processors Association, the North American Millers' Association, the Corn Refiners Association, the National Corn Growers Association, the National Grain and Feed Association, the Biotechnology Industry Association, and a number of other technology providers.

As you are aware, on 29 September 2000 Aventis announced that it would not market StarLink™ corn in the year 2001. As a further assurance of this action, Aventis voluntarily cancelled the registration for Cry9C StarLink™ corn on 12 October 2000. Therefore, there is a finite potential amount of the Cry9C protein to which this addendum refers.

Aventis CropScience USA, LP.
2 T W Alexander Dr., Research Triangle Park, NC 27709, Telephone: (919) 549-2000, Fax: (919) 549-3929

The enclosed updated safety assessment was prepared accounting for the corn that may have entered the food channels from the 1999 and 2000 growing seasons. This assessment draws on new information and data to provide a comprehensive, weight of the evidence evaluation. New information and data include the assessment, itself, and a comparative evaluation of the potential allergenicity of Cry9C protein relative to food allergens generally, and relative to peanut allergens specifically. In addition, the following recently completed studies provide useful data for assessment purposes:

- Cry9C protein: The digestibility of the Cry9C protein by simulated and intestinal fluids, MRID # 45114401.

- The comparison of the *in vitro* digestibility based upon pH of the endotoxin Cry9C derived from *Escherichia coli* and *Bacillus thuringiensis*, MRID # 45114402.

- Evaluation of IgE antibody reactivity of food-allergic subjects to StarLink™ corn submitted to EPA 10/24/00.

- Preliminary study for the detection of Cry9C protein in taco shells. FIFRA 6(a) (2) report, submitted to EPA 10/16/00.

- Analysis of taco shells for Cry9C protein submitted to EPA 10/24/00.

- Preliminary report on the detection of CBH 351 DNA in taco shells: investigations carried out between the afternoon of September 22 and the morning of 28 September 2000. FIFRA 6(a) (2) report submitted to EPA 10/16/00.

- Further studies on determination of CBH 351 DNA in taco shells: investigations carried out between the afternoon of September 28 and the morning of 29 September 2000. FIFRA 6(a) (2) report submitted to EPA 10/16/00.

A very conservative approach was used to evaluate exposure and potential health risk to the US consumer that might result from the possible presence of Cry9C protein in food products. Based on this assessment, there is very strong support for the conclusion that the Cry9C protein meets the Food Quality Protection Act "reasonable certainty of no harm" standard. To ensure that any StarLink™ corn in the food channels is cleared through the various processing and commercial channels a four year time-limited tolerance exemption is being requested (see enclosed communication).

On 20 November 1998 Aventis (formerly AgrEvo USA Company) submitted a petition proposing to amend 40 CFR 180.1192 to establish exemptions from the requirement of a tolerance for both food and feed uses for the plant-pesticide described above. The EPA has granted to AgrEvo (formerly Plant Genetic Systems (America), Inc.) an exemption from the requirement of a tolerance (22 May 1998) for animal feed uses of this material.

Should you have any queries or concerns Aventis is available at any time to discuss this further and will make industry experts available for such discussions. Please feel free to contact me at (919) 549-2379, fax (919) 549-3929 or email sally.vanwert@aventis.com.

Sincerely,

Sally Van Wert

Sally Van Wert, Ph.D.
Director, Regulatory Affairs –Biotechnology
North America

Attachment (Timeline Justification)
Enclosures (EPA Form 8570-1; 3 copies of Volume 1)

VOLUME #	**FIFRA DATA REQUIREMENT**	TITLE	**MRID#**
1	Not Applicable	Updated Safety Assessment of StarLink™ Corn Containing Cry9C Protein	

ATTACHMENT

Justification for the 4 year timeline being requested for a temporary exemption from the requirement of a tolerance for the Cry9C protein in food products. (Per communication from the Grocery Manufacturers of America to Aventis CropScience USA LP, 23 October 2000.)

1. One year to clear the 1999 crop from bin bottoms in the summer/fall of 2001 (October 2001)

2. 1-2 months to go through mills and plants into consumer packages (December 2001)

4. 1 year shelf life in the retail distribution system (December 2002)

5. Add 6 months for longer-shelf products (frozen/other) (July 2003)

6. Add 2-3 months in the consumer pantry (October 2003)

7. Add one year for 2000 crop (October 2004)

VOLUME 1 of 1

STUDY TITLE:
Updated Safety Assessment of StarLink™ Corn Containing Cry9C Protein

DATA REQUIREMENT:
Not Applicable

AUTHORS:
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STUDY COMPLETED ON:
October 24, 2000

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PROJECT IDENTIFICATION:
STARLINK™ 00-01

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this report on the basis of its falling within the scope of FIFRA Section 10 (d)(l)(A),(B), or (C).

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SPONSOR REPRESENTATIVE: ______________________________

Sally Van Wert, Ph.D. Date
Director
Regulatory Affairs-Biotechnology North America
Aventis CropScience USA, LP

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The following information is not subject to the principles of 40 CFR 160, GOOD LABORATORY PRACTICE STANDARDS (FIFRA), as promulgated in *Federal Register*, 54, No. 158, 34067-34704, 17 August 1989. Several studies used as references for this document, however, were conducted in accordance with the appropriate GLP standards as verified by the GLP compliance statements found in these reports.

AUTHOR:

Nancy J. Rachman, Ph.D. Date
Director, Food Practice
Novigen Sciences, Inc.

SPONSOR & SUBMITTER:

Sally Van Wert, Ph.D. Date
Director, Regulatory Affairs-Biotechnology North America
Aventis CropScience USA, LP

QUALITY ASSURANCE STATEMENT

REPORT TITLE: Updated Safety Assessment of StarLink™ Corn Containing Cry9C Protein

REPORT IDENTIFICATION: StarLink™ 00-01

This report was audited and reviewed with respect to the study data and the residue files used for the exposure assessment. The data summary tables were derived using an electronic spreadsheet (Excel®). The results of the formulae used in the spreadsheet were independently verified. The information in the text of the report is representative of the data tables; the report contents accurately reflect the data.

Auditor: Beth M. Polakoff, MBA — Date
Director, Regulatory and Business Strategy
Novigen Sciences, Inc.

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UPDATED SAFETY ASSESSMENT OF STARLINK™ CORN CONTAINING CRY9C PROTEIN

I. PURPOSE

The purpose of this document is to determine if, and at what level, Cry9C protein poses a food allergenic potential. The analysis is provided by an updated safety assessment of StarLink™ corn containing Cry9C protein. Specifically, drawing on new data and information, this document provides a comprehensive weight of the evidence analysis of all available information and data.

II. INTRODUCTION

A. Background

StarLink™ corn was registered in 1998 for use by the US Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for use as animal feed and for industrial uses (production of ethanol, for example). In granting that registration, EPA concluded that Cry9C protein and related DNA met the safety standard under the FQPA for use in field corn for animal feed use. That is, EPA concluded that “based on the toxicology data cited and the limited exposure expected with animal feed use, there is reasonable certainty that no harm will result from aggregate exposure to the US population, including infants and children” (US EPA Bt Plant-Pesticides Biopesticides Registration Action Document, page IIB18, EPA Scientific Advisory Panel (SAP) website, October 2000 science assessment document). The EPA and the EPA’s SAP were not able to conclude that the Cry9C protein was or was not an allergen (FIFRA SAP Report, Session I – A Set of Scientific Issues being Considered by the Environmental Protection Agency Regarding: Food Allergenicity of cry9C Endotoxin and other Non-digestible Proteins, page 8, June 2000) and, thus, registration for human food use has not yet been granted.

StarLink™ corn is a variety of corn modified through traditional and well-recognized techniques of genetic modification to contain the plant pesticide *Bacillus thuringiensis* (“Bt”) subspecies *toliworthi* Cry9C protein and the genetic material necessary for the production of the protein (DNA). Bt proteins have insecticidal properties and have been used commercially for more than thirty years. Among these products are microbial sprays (Agree, XenTari) with the Cry9B protein, which is highly homologous with the Cry9C protein. Corn plants with the Bt protein have been widely and safely used for a number of years. These products thus have a long history of safe use.

Pursuant to the registration, StarLink™ corn was planted in 1998, 1999 and 2000. Approximately, 10,000 acres were planted in 1998, 250,000 acres were planted in 1999, and 350,000 acres were planted in 2000 out of the approximately 80,000,000 acres of corn planted in the United States in each of those years. Although StarLink™ corn was not registered for use in human food, it now appears that through means not well known, not all of the corn has been kept within the scope of the registered uses (animal feed and non-food industrial uses). The significance to human health of the potential presence of the Cry9C protein and/or the DNA in human food is the subject of this analysis. The analysis relies on the best available data and information and conservative assumptions to assess the potential risks to human health, if any.

B. Approach of the Analysis

Human health assessments typically involve an evaluation of the potential hazard of the material in question and an evaluation of the magnitude of potential exposure to the material. The analysis set forth in this document follows that approach.

First, it identifies the material of potential concern. In the case of StarLink™ corn, the only component of the corn that presents any potential for human health concern is the Cry9C protein and, only then, with regard to the potential for it to cause an allergic reaction in sensitized individuals. The EPA stated that there are no issues relative to the safety of food containing StarLink™ other than the potential allergenicity issue.

Concerning the allergenicity question, this assessment provides a comprehensive review of all available information and data and concludes that Cry9C is not an allergen.

After addressing the data and information pertinent to assessing the question of whether the Cry9C protein is likely to be an allergen, the analysis then turns to an assessment of the potential amount of the protein to which humans might be exposed. This analysis takes into account available information about: (1) the amount of StarLink™ corn planted in 1999 and 2000 and the known or probable disposition of that corn; (2) quantity of Cry9C protein in corn; (3) the quantity of corn contained in different food products; (4) the fate and disposition of Cry9C protein in food; (5) quantity of various foodstuffs which contain corn consumed by various population subgroups; and (6) other relevant data.

This assessment considers the risk of adverse allergic responses as a result of a very low level and temporary dietary exposure to Cry9C protein. The strongly supported conclusion is that Cry9C is not an allergen. Furthermore, the assessment strongly concludes that even if Cry9C protein were allergenic, the low level and temporary exposures would neither sensitize individuals nor elicit an allergic response in sensitized individuals. The full basis for these conclusions is set forth below.

C. Context for the Assessment

In order to evaluate properly the potential human health consequences of the presence of Cry9C protein in human food, one must understand how corn is harvested and how it moves through various steps in the distribution chain before it is ultimately used in the production of food for human consumption. With that information, it becomes apparent that there is substantial dilution at each stage of the movement of corn from the farm to the table. To put it differently, the corn from one field or farm is commingled at each stage of the process with corn from other fields and farms.

This section sets forth a brief summary of that information. A full explanation of whole corn handling and grain processing at dry mills is contained in Appendix 1, Corn Handling and Grain Handling Discussion prepared by the North American Millers Association and the National Feed and Grain Association.

Whole Corn Handling Operations from Farm to Elevator

Virtually all farmers harvest corn with a combine equipped with a corn header and transfer the harvested grain from the combine to a truck to deliver either to on-farm storage, a feedlot, or a commercial grain elevator. Farm trucks today typically hold 200 to 800 bushels with the average size about 400 bushels.

When the grain is delivered to a local elevator, it is dumped into a pit. From the pit, the grain is normally conveyed via a bucket elevator to the top of grain storage bins where it is dropped to the bottom of the bin, or onto other grain. Bin sizes at country elevators generally range from 10,000 bushels to 1,000,000 bushels with an average of 70,000 to 80,000 bushels.

Throughout this grain handling process, there is a continuous blending and commingling of the corn from any one farm. The farm truck often carries corn taken from different fields on the farm. When the farm truck arrives at the elevator at harvest, it is frequently one of many trucks in line to dump. In the binning of the grain, the contents of each truck are dumped on top of each other in continuous fashion.

As grain is dropped from the top of storage bins at the elevator, the grain forms an inverted conical shape, as the grain enters at the center and flows out to the sides of the bin. There is a “layering” effect of the grain from each individual truck.

When the grain is drawn from the bottom of the bin, a different flow pattern develops. The grain flowing out will form a "core" in the center. The center portion of the grain bin flows out first, then a cone develops, with the upper portions of the grain flowing out toward the early part of the removal process. As the bin empties, the grain at the sides of the bins starts to flow out of the bottom.

All the truck deliveries used to fill the bin are commingled in the storage/handling process. The degree of mixing of the grain will depend in part on the point at which the truck was dumped. Commingling further occurs as elevators often draw from multiple bins in order to "blend" grain for loading into one transport conveyance to meet quality specifications of different customers.

If an average farm truckload of 400 bushels of pure StarLink™ corn were to be delivered to an elevator and placed into even a small 10,000 bushel bin, a commingling/dilution of that grain on the order of 3 to 5 times is a conservative expectation, with 3 probably a "worst case" situation (Appendix 1, Corn Handling and Grain Handling Discussion prepared by the North American Millers Association and the National Grain and Feed Association).

Grain Processing at Dry Mills

Grain is delivered from elevators to dry corn mills via trucks or rail cars. Trucks typically haul 1,000 bushels with rail cars holding about 3,500 bushels. The initial receiving process is much like that at the elevator, dumping into a pit and elevating grain into storage bins, which hold the grain until it enters the processing stream.

Most dry corn mills are continuous process (rather than batch). Because the grain in a milling operation is being continuously mixed through tempering, milling, and handling, the degree of dilution at any one stage is probably much greater than the factor of three, considered to be the "worst case" at the elevator. Assuming conservatively that there are only seven handling and processing operations, each of which is assumed to dilute the grain by a factor of three, suggests that one truckload of pure StarLink™ corn would be diluted by several orders of magnitude, prior to reaching the food processor or consumer.

Wet Milling

Corn is received at wet milling plants via truck, railcar, or barge. Corn is stored at wet mills in a manner similar to dry mills or grain elevators.

The corn wet milling process separates corn into four basic components: starch, germ, fiber and protein. There are five basic steps to accomplish this process. All processes in corn wet milling are continuous (rather than batch).

Incoming corn is inspected and cleaned. It is then steeped in a dilute sulfurous acid solution for 30 to 40 hours. This results in the breaking of the starch and protein bonds. The next step in the process involves coarse grind, which separates the germ from the rest of the kernel. Corn germ is subject to mechanical and solvent extraction to remove oil, which is then refined through degumming, alkali treatment, bleaching, winterization, and vacuum steam stripping deoderization. The remaining slurry consisting of fiber, starch and protein is finely ground and screened to separate the fiber from the starch and protein. Fiber is combined with the water from corn steeping to produce corn gluten feed. The remaining starch and gluten are separated into hydrocyclones. The separated gluten is dried to produce corn gluten meal. The remaining starch is repeatedly washed in fresh water. Water from this washing step flows back through the process countercurrently to the flow of corn. The starch is then converted to sweetners or fermentation products or dried and packaged as starch (Blanchard, 1992). Of the wet milled corn, approximately 60 percent is directed toward sweetner production, 25 percent toward alcohol production, and 15% toward starch production. In the latter case 80 percent is directed toward industrial purposes while the remaining 20 percent is used in food starches (Personal communication, Corn Refiners Association).

As in the case of the dry milling discussion, commingling of corn occurs. It is estimated that one truckload of pure StarLink™ corn would be diluted by several orders of magnitude, prior to reaching the food processor or consumer. This extensive processing likely leads to, at least, degradation of protein.

D. Safety of *cry9C* DNA and DNA Generally

With respect to the safety of c*ry9C* DNA and DNA in general, EPA has concluded that:

DNA is common to all forms of plant and animal life and the Agency knows of no instance where these nucleic acids have been associated with toxic effects related to their consumption as component of food. These ubiquitous nucleic acids as they appear in the subject plant pesticide have been adequately characterized by the applicant and supports (sic) EPA's conclusion that no mammalian toxicity is anticipated from dietary exposure to the genetic material necessary for the production of the Cry9C protein. (63 Fed. Reg. 28259; 5/22/98).

There is an EPA proposed exemption from the requirement of a tolerance for nucleic acids produced in plants as part of a plant-pesticide (Plant Pesticides; Subject to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA): Proposed Rule, 59 Fed. Reg. 60505; 11/23/94). This proposal states:

> *Residues of nucleic acids produced in living plants as part of a plant-pesticide active or inert ingredient, including both deoxyribonucleic acid and ribonucleic acids, are exempt from the requirement of a tolerance.*

More recently, EPA confirmed its views concerning the safety of nucleic acid in its background materials from the October 18-20, 2000 SAP meeting; Biopesticides Registration Action Document: Bt Plant-Pesticides (http://www.epa.gov/scipoly/sap/).

> *DNA is common to all forms of plant and animal life and the Agency knows of no instance where these nucleic acids have been associated with toxic effects related to their consumption as a component of food.*

In addition, the US Food and Drug Administration (FDA) has also concluded that DNA is generally recognized as safe (1992, FDA Food Policy).

Based on these EPA and FDA statements, the presence of *cry9C* DNA in food is not relevant to the safety assessment of StarLink™ corn because it is recognized as safe.

E. Assessment of Potential Toxicity of Cry9C Protein

Based on the history of the use of Bt microbial pesticides and available toxicity data on Cry9C protein, it is reasonable to conclude that, other than possible allergenicity, there are no toxicity issues related to the food and feed use of Cry9C protein. EPA concurs with that conclusion.

In the final rule establishing the exemption from the requirement of a tolerance for Cry9C protein and genetic material in feed EPA stated:

> *Bt microbial pesticides, containing Cry proteins other than Cry9C, have been applied for more than 30 years in food and feed crops consumed by the US population. There have been no human safety problems attributed to the specific Cry proteins. An oral dose of the tryptic core Cry9C protein of at least 3,760 mg/kg was administered to 10 animals without mortality demonstrating a high degree of safety for the protein. (63 Fed. Reg. 28258; 5/22/98).*

The lack of acute oral toxicity of Cry9C protein is consistent with the lack of toxicity and established safety of other Cry class proteins previously approved for use by the Agency. Furthermore, additional toxicity studies submitted to EPA support this conclusion (*MRID #44734302 and 44734303).* Thus, general toxicity issues are not considered further in this assessment.

F. Assessment of Potential Allergenicity of Cry9C Protein

Given that DNA is recognized as safe, and that there are no general toxicity issues related to Cry9C protein, the only remaining issue relative to the safety of StarLink™ corn is the potential allergenicity of Cry9C protein and the associated level of potential risk.

In regard to the use of StarLink™ corn in animal feed, the EPA concluded that:

> *The Cry9C protein would not likely cause an allergic reaction to man when used in feed corn because; (1) it was not from allergenic sources and (2) the best available information indicates that edible products derived from animals such as meat, milk and eggs intended for human consumption, have not been shown to be altered in their allergenicity due to changes in the feed stock utilized. (US EPA Bt Plant-Pesticides Biopesticides Registration Action Document, page IIB18, EPA Scientific Advisory Panel website, October 2000 science assessment document.)*

This document provides a brief background on food allergy and, drawing on new information and analysis, provides a risk assessment regarding the potential allergenicity for StarLink™ corn expressing Cry9C protein in food. A discussion of the new information relevant to the allergenic potential of the Cry9C protein is also included. Based on a review of all available information and data, this assessment concludes that there is a reasonable certainty that Cry9C protein is not an allergen, and is not likely to become an allergen even if there were long-term consumption.

In an independent review by Dr. S.L. Hefle of the Food Allergy Research and Resource Program, University of Nebraska, Dr. Hefle concluded that "the data shared by Aventis, taken in total, while not conclusive provide evidence that (sic) of low probability of allergenicity of Cry9C" (Appendix 2). A written statement submitted by Dr. S.L. Taylor of the same organization to EPA's SAP (October 20, 2000) supports this conclusion (Appendix 3).

G. Food Allergens and the Use of the Peanut for Comparison Purposes

Food allergy affects 1-2% of adults and 6-8% of children in the United States (Sampson, H.A. *et al.,* 1996; Metcalfe, D.D. *et al.,* 1996). Protecting food allergic patients from unexpected exposure to food allergens is a critical priority. Food allergy assessments ensure that food allergic patients are protected from unexpected exposure to the allergens that might cause them harm. In addition, food allergy assessment evaluates the potential of any new protein to become a new allergen, and to create a newly sensitized population.

In his written submission to the SAP (October 20, 2000), Dr. S.L. Taylor stated that sensitization to foods requires multiple exposures over an extended time period and at a relatively high percentage of total protein content (Appendix 3).

For StarLink™ corn, there is no history of significant consumption, and hence no real potential for allergic sensitization. Furthermore, based on available data and information, the amount of Cry9C protein that could potentially be present in corn products would be present at levels far below those required to cause sensitization. Therefore, it is reasonable to conclude that there are not now and will not be in the future any "at risk" consumers. Furthermore, the EPA has previously concluded that after more than 30 years of commercial use of microbial products containing a variety of Cry proteins, including proteins from the Cry9 class, no allergy has been attributed to Cry proteins (McClintock *et al.,* 1995; EPA, 1999).

Most allergenic proteins are present in levels of 1 to 40% of the total protein of the allergenic food (Metcalfe, D.D., *et al.,* 1996 ; Yunginger, J.W *et al.,* 1997; Li-Chan, E. and Nakai, S., 1989; Murphy, P.A. and Resurrection, A.P., 1984; Kalinski, A. *et al.,* 1990; Carpentier, B.A. and Lemmel, D.E., 1984; Goldberg, R.B. *et al.,* 1983; Burks, A.W. *et al.,* 1992; Lotan, R. *et al.,* 1975; Crouch and Sussex, 1981). In contrast, there is an extremely low percentage (0.0129%) of the Cry9C protein in StarLink™ corn grain (Table 1) (*MRID #45025701*).

Even lower levels of Cry9C protein might be expected in foods containing corn as an ingredient since, following dry or wet milling, the protein is redistributed into individual commodities. Thereafter food processing exposes the protein to a range of potential degradation procedures which in some instances could completely destroy the protein. In taco shells, for example, no protein was detected (Preliminary Study for Detection of Cry9C Protein in Taco Shells, FIFRA 6(a)(2) report, submitted to EPA on 10/16/00; *MRID #44384301* and Analysis of Taco Shells for Cry9C Protein submitted to EPA on 10/24/00).

TABLE 1

QUANTITIES OF CRY9C PROTEIN IN PROCESSED COMMODITIES OF STARLINK™ CORN (CBH351) EXPRESSED AS PERCENT OF CRUDE PROTEIN (*MRID #45025701*)

Process	Commodity	Crude Protein (All Types) in Matrix (%)[a]	% Cry9C in Crude Protein	
			Transgenic Unsprayed[b]	Transgenic Sprayed[b]
	Whole corn	8.9 – 10	0.0116	0.0129
Dry Mill	Composite Grits	7 - 10.3	0.00861	0.0111
	Hull Material	8	0.0130	0.0163
	Meal	7.5 - 9.0	0.00989	0.0118
	Flour	5.2 - 7.8	0.0149	0.0147
	Solvent Extract Germ	12 – 25	0.0345	0.0298
	Crude Oil	0	NA[c]	NA
	Refined Oil	0	NA	NA
Wet Mill	Steepwater Concentrate	41 – 62	0.000034	0.000078
	Hull Material	8	0.00719	0.0146
	Gluten	41 – 60	0.00015	0.00011
	Starch	0.6	NA	NA
	Solvent Extracted Germ	22.6	0.00056	0.00063
	Crude Oil	0	NA	NA
	Refined Oil	0	NA	NA

[a] Range of data from Wolff, I.A. 1982; Ensminger, M.E. *et al.*, 1990; McGregor, C.A. 1994.
[b] Unsprayed = Not treated with Liberty® Herbicide
[b] Sprayed = Post emergent treatment with Liberty® Herbicide
c NA - concentration was below limit of quantitation (LOQ) for these samples.

Since allergy to Cry9C protein does not already exist, the extremely low level of Cry9C protein estimated to be consumed using a reasonable, worst case exposure assessment leads to the conclusion that the Cry9C protein present in StarLink™corn is very unlikely to become an allergen.

Peanuts account for the majority of fatal and near-fatal, food-induced, anaphylactic reactions in the United States (Yunginger JW, *et al.*, 1988; Li, X-M, *et al.*, 2000). About 1.5 million Americans (Li, X-M, *et al.*, 2000) are allergic to peanuts. Given the severity, prevalence, and frequently lifelong persistence of peanut allergy, a comparison of the potential allergenicity of a new protein, such as Cry9C protein, with peanuts, one of the most potent known human food allergens, provides an extremely conservative and protective assessment.

III. HAZARD ASSESSMENT

Based on data previously submitted to EPA by Aventis CropSciences USA, LP (Aventis), and based on new information and data described below, it is clear that Cry9C protein has a very low potential of becoming a food allergen. The Cry9C protein does not match the physicochemical characteristics of known food allergens. Results from an oral, 30-day repeated dose study in mice demonstrated no immunological effects at any dose level (*MRID #44734303*). The newly introduced protein in StarLink™ corn has been shown not to alter the endogenous levels of allergens in corn compared to traditional corn varieties (*MRID #44384405*), and the Cry9C protein does not cross-react with sera from patients allergic to other major allergenic foods (Aventis report submitted to EPA on 10/24/00). Finally, the minute levels of Cry9C estimated to be consumed using a reasonable, worst case assessment are orders of magnitude below the levels of allergenic proteins in foods to which people have become sensitized. Based on the following analysis of potential risk, it is clear that the presence of Cry9C protein in food meets the "reasonable certainty of no harm" safety standard under the Food Quality Protection Act (FQPA); there is a reasonable certainty that Cry9C protein is not and will not become an allergen.

A. Physiochemical Characteristics of Cry9C Protein

To assess the potential allergenicity of a protein, it is useful to compare the physicochemical properties of that protein to known food allergens. Properties such as the structural similarity of a new protein compared to known food and other allergens, stability, and proteins levels in food are typically considered (Metcalfe *et al.*, 1996).

Data developed by Aventis support the conclusion that the Cry9C protein has a very low potential of being a food allergen. The data on the parameters to assess the potential for the Cry9C protein to induce sensitization are:

The *cry9C* gene was obtained from a common soil bacteria, *Bacillus thuringiensis*, which has no known capacity to cause allergies;

1. Cry9C protein lacks structural similarity to any known allergen (food and others). That is, the amino acid sequence of Cry9C protein is not similar to the amino acid sequence in any other known allergen (*MRID #44258109 and 44384404*);
2. Cry9C is not glycosylated in StarLink™ corn in contrast to known allergens (*MRID #44384401*);
3. Cry9C is expressed at extremely low levels (0.0129%) in corn grain relative to known food allergens (*MRID #45025701*); and
4. Based on the results of recent digestibility studies conducted under simulated gastric conditions as defined by the US Pharmacopoeia, Cry9C protein digests within the range of normal human gastric pH and gastric emptying time (*MRID #45114401 and 45114402*).

B. 30-day Repeated Dose Mouse Study

Aventis conducted a 30-day repeated dose study in mice. There were no immunological effects observed at any dose level. Endpoints included an examination of the immune system, blood parameters, reticuloendothelial elements of the bone marrow, and lack of protein binding to villi and crypt cells of the small intestine. Lymphatic tissue of the intestines (i.e., Peyer's patches), the spleen, submandibular glands, mesenteric lymph nodes and thymus were all normal upon microscopic examination (*MRID #44734303*) .

C. Molecular Genetic Effects on Endogenous Corn Allergens

Introduction of the c*ry9C* gene and expression of the Cry9C protein into StarLink™ corn did not alter or enhance the intrinsic allergenic status of corn. Through the technique known as RAST (radioallergosorbent test), it was demonstrated that the serum from corn allergic individuals reacted equivalently to the endogenous allergens in StarLink™ corn and conventional corn. Statistical analysis revealed no significant differences, indicating no differences in the quantity and reactivity of endogenous corn allergens as a result of genetic modification. *(MRID #44384405).*

D. Cross Reactivity

Because it is known that people who are sensitive to known food allergens in food may also react to other food proteins, even without previous exposure, RAST tests were performed to determine if individuals allergic to the well-known human food allergens wheat, rice, buckwheat, soy, peanut, milk, eggs, and shrimp demonstrated cross-reactivity to Cry9C. This study demonstrated a lack of cross-reactivity of the serum from these food-allergic patients to the Cry9C protein, which is consistent with and supports the lack of structural and immunological similarity of Cry9C protein to important food allergens, and provides additional evidence of the low probability that Cry9C is a food allergen. (Aventis preliminary report to EPA on 10/24/00.)

E. Protein Abundance and Potential Allergenicity

It is unlikely that a protein, which is present at low levels in the diet, would become a food allergen (Metcalfe, D.D. *et al.*, 1996; Fuchs, R.L. and Astwood, J.D., 1996; Taylor, S.L., 1992; Hefle, S., 1996; Gendel, S.M., 1998). The induction of all immunological responses is complex, but induction (i.e., becoming sensitized) is clearly dose dependent. A raw food product like soybean flour will contain thousands of different proteins, but most are present at very low concentrations. Allergic responses are not induced by these minor components, but are specific for a few usually highly expressed proteins (Yunginger, 1997; Astwood *et al.*, 1996; Metcalfe *et al.*, 1996).

A rough estimate of consumption of various allergens on an average per serving basis for 2 to 4 year old children is shown in Table 2, and is based on both the total protein and specific major allergen content in foods (Yunginger, 1997; Astwood *et al.*, 1997). This comparison supports the conclusion that important food allergens tend to be relatively abundant in food, and therefore they are consumed at relatively high levels. Conversely, based on this information and the references noted above, it is generally accepted that a protein present at very low levels in food represents a minimal potential for allergic sensitization.

TABLE 2

ESTIMATE OF CONSUMPTION OF VARIOUS ALLERGENS ON AN AVERAGE PER SERVING BASIS FOR 2 TO 4 YEAR OLD CHILDREN

FOOD (SERVING SIZE) [TOTAL PROTEIN]	ALLERGENIC PROTEIN	STRONG/WEAK FOOD ALLERGEN (++, +/-, -)	% OF TOTAL PROTEIN	ALLERGEN /SERVING (MG)
Cow's milk (250 ml)	β-lactoglobulin	++	9	800
[9 g]	α-caseins	++	34	3050
	α-lactalbumin	++	4	350
Soybean (milk 250 ml)	11s glycinin	++	51	2080
[4.2 g]	7s β-conglycinin	++	18.5	770
	Lectin	+/- or -	1	42
	Kunitz trypsin inhb.	+/- or -	2	84
Peanut (butter 32g)	Ara h1	+++	10	800
[8 g]	Ara h2	+++	6	480
Chicken egg (58 g) [white =3.5 g]	Ovomucoid	+	11	385
	Ovalbumin	+	54	1900
Brazil nut (2 g) [1 g]	2s albumin	++	10	100

(Table based on a combination of Astwood J, *et al.*, 1997 and Yunginger, 1997)

In contrast to major food allergens (table above) which are typically at high dietary levels (greater than 1% of total protein), the percent of Cry9C protein in StarLink™ corn is approximately 1/80th as abundant (i.e., almost 2 orders of magnitude lower). Therefore, Cry9C protein as produced in StarLink™ corn does not share this important attribute, abundance, with food allergens.

These factors (physiochemical characteristics, immunotoxicity data, molecular genetic effects, cross reactivity and allergen abundance) taken together demonstrate that Cry9C protein and StarLink™ corn share none of the hazard characteristics associated with important food allergens and allergenic foods.

IV. SAFETY ASSESSMENT

A. Potential Dietary Exposure to Cry9C Protein

The potential dietary exposure to Cry9C protein is an important consideration with respect to evaluating the potential for Cry9C to be an allergen. As allergenicity expert Dr. S. L. Taylor, University of Nebraska, noted in a written statement submitted to EPA's FIFRA SAP (October 20, 2000):

In order for people to become allergic to a protein they must be exposed to it multiple times over an extended period until they become sensitized. The protein must also be present at a relatively high percentage of total protein content. Most allergenic proteins are present at levels of 1 to 40 percent. Aventis indicates that the Cry9C protein is present in corn grain at 0.013 percent, but any taco shells would contain far less due to the presence of other varieties of corn and the use of other ingredients. *(See Appendix 3 for complete letter.)*

Since multiple exposures over an extended period of time to relatively high levels of protein are known to be required to produce sensitization, the potential for dietary exposure to Cry9C in corn-containing foods is an important consideration. The issue of levels of Cry9C protein potentially present in corn is what we address here.

The analysis has two parts. First, the potential dietary exposures to (or intakes of) Cry9C, per day, from StarLink™ corn were estimated for the US population and selected subgroups, using 1999 and 2000 production data and reasonable worst-case approaches, inputs and assumptions. Second, these estimated potential intakes of Cry9C were compared to levels of peanut allergens in peanut butter. Peanut allergens Ara h1 and Ara h2 were used as a conservative basis for comparison because peanut allergy is prevalent (1.5 million Americans according to Li X.-M. *et al.*, 2000), severe (peanut allergens cause the most fatal and near-fatal anaphylactic reactions, according to Yunginger *et al.*, 1988; Li X.-M. *et al.*, 2000; Bock 1988) and because there is no curative therapy (Li X.-M. *et al.*, 2000).

The approach, including an explanation of the different scenarios, is discussed in detail here. Results of the analyses are presented in Tables 3-6.

The potential for exposure to Cry9C protein in corn-containing foods, in any given year, depends on all of the following factors. Therefore, the assessment takes all of these factors into account:

- ♦ The percentage of corn grown in that is StarLink™;
- ♦ The percentage of StarLink™ corn potentially entering food channels;
- ♦ The protein content of foods made from corn;
- ♦ The percentage of protein in those foods that is Cry9C; and
- ♦ The dietary intake of foods potentially containing Cry9C.

The data inputs that have been selected for each of these factors for 1999 and for 2000 are explained in detail in the following sections. 1998 was not included in this analysis, since even if all StarLink™ had gone to food use the levels in the food supply would have been insignificant. Ten thousand acres were planted in 1998, yielding 1.5 million bushels. This amounts to 0.013% of the corn supply in the 1998-98 market year (11,085 million bushels, according to USDA ERS statistics [Feed Outlook Oct. 2000, 10/16/00, Table 1]).

1. Percentage of corn grown that is StarLink™

2000 crop year**.** Of a total corn acreage of 79.57 million acres (NCGA 9/30/00), 0.35 million acres of StarLink™ were planted, or 0.4% of total corn acreage. This value of 0.4% is used in the year 2000 Tables 3 and 4 as the "% Acres of StarLink™ corn in US."

1999 crop year**.** Total corn acreage planted was 77.43 million acres (NCGA 9/30/00), 0.25 million were StarLink™, or 0.3%. This value of 0.3% is used in the year 1999 Tables 5 and 6 as the "% acres of StarLink™ in US."

2. Percentage of StarLink™ corn potentially entering food channels.

Corn is a highly blended commodity. There are many steps between farm and finished food in which multiple opportunities for mixing corn from difference sources exist (see Appendix 1). The probability of a truckload of a commodity like corn containing the Cry9C protein remaining a distinct batch through the steps in the production system and resulting in a batch of corn-containing product with high levels of Cry9C is highly improbable and ignores the realities of commodity handling and food processing. The exposure assessment scenarios therefore assumed that in the reasonable worst case, StarLink™ corn moves in the food system like any other corn without any feed-use only restrictions. Given the conservatisms built into the inputs used for the various exposure factors in the assessment, and the lack of hazard associated with Cry9C, the approach is appropriate and protective.

<u>2000 crop year</u>. Three different approaches were used to estimate the percentage of StarLink™ corn entering food channels. The approaches resulted in estimates of 12 or 50%, as follows.

- ***12%***. (Used in analysis presented in Table 3) Aventis has determined, through one-on-one interviews with growers, that 88% of the StarLink™ corn produced is still either on the farm for animal feed use or is documented as being at feedlots. One half of the remaining 12% has potentially been directed to food uses (Aventis communication to USDA). To be conservative, the 12% figure is used in the assessment. (This 12% corresponds to 9.6 million bushels.)
- ***50%***. (Used in analysis presented in Table 4) This assumes that corn has an equal chance of being used for feed or food, although USDA data indicate that most corn goes to non-food channels (see under 1999, below). As discussed below in more detail, the majority of the corn produced in the year 2000 actually went into non-food uses.
- ***50%.*** (Used in analysis presented in Table 4) In the 2000 crop year, 350,000 acres of StarLink™ corn were planted; this represents 0.4% of the total US corn acreage (80 million acres). Buffer zones of 660 ft. were required for StarLink™ plantings. Because these buffer zones could contain corn (non- StarLink™) and because some of this corn could be cross-pollinated by StarLink™, this scenario accounts for the contribution of buffer acreage to the percentage of corn by increasing the percentage of StarLink™ corn entering food channels <u>from 0.4% to 50%</u>. This is an extreme overestimate for the following reasons: (1) Not all buffer acreage is planted to corn. Aventis has been conducting one-on-one interviews with growers. These interviews are not completed, but thus far Aventis has determined that 168,000 buffer acres were planted to corn. (2) Not all corn in buffer zones will be cross-pollinated by StarLink™ corn and contain Cry9C. Jemison and Vayda (2000) reported that "cross-

pollination of commercial maize cultivars at 100 ft. downwind from the source of genetically modified maize was 1%, and this proportion declined exponentially to 0.1% at 130 ft. and further declined to 0.03% at 160 ft." As mentioned, EPA requires a 660 ft. buffer for StarLink™.

1999 crop year. In the absence of specific data on disposition of the 1999 crop of corn, three different assumptions were used to estimate the percentage of StarLink™ corn entering food channels. The approaches resulted in estimates of 13 or 50%, as follows.

- ***13%.*** (Used in the analysis presented in Table 5) This realistic worst-case number was calculated from USDA ERS statistics (Feed Outlook Oct. 2000, 10/16/00, Tables 1 and 5). The approach rests on the assumption that a corn grower who planted but StarLink™ corn but did not follow instructions would most likely treat (i.e., harvest and sell) StarLink™ just like any other yellow corn variety. Therefore, StarLink™ would move into food vs. feed channels in the same proportion as other yellow corn.

According to USDA statistics for crop year 1999 which includes leftover and remaining 1998 stocks, 9,437 million bushels were produced and 1,787 million bushels were remaining from prior production. Of this total 11,224 million bushel supply, 1,913 million bushels were directed to food and industrial uses (Food Seed Industrial, FSI, in USDA Table 1). However, the FSI category includes 565.8 million bushels for fuel alcohol production, which is not relevant for this analysis. 129.7 million bushels go to beverage alcohol production. According to the USDA Nutrient Database, alcoholic beverages distilled from corn grain do not contain protein. Therefore, these uses were also excluded from the analysis. The calculation of the percentage of StarLink™ corn that is potentially in the food supply is therefore the realistic worst-case percentage of StarLink™ in food channels in 1999.

$$\frac{(1913) - (565.8 + 129.7)\text{ mbu}}{11{,}224\text{ mbu}} = 0.108 = \underline{11\%}$$

If prior year carryover is excluded from 1999 supply, the calculation is:

$$\frac{(1913) - (565.8 + 129.7)\text{mbu}}{9437\text{ mbu}} = 0.129 = \underline{13\%}$$

- ***50%***. (Used in the analysis presented in Table 5) This assumes that corn has an equal chance of being used for feed or food, although available data indicate this is not actually true, as discussed.

3. Protein content of foods made from corn

Corn in food channels is either wet-mill processed, which produces high fructose corn syrup (HFCS), glucose, dextrose or starch, or dry-milled, which produces cereals and other products including corn meal and flour. The dry-milled fractions (corn meal and flour) contain 5-9% crude protein (USDA Nutrient Database) [MRID No. 45025701]. For purposes of these analyses, we used the higher value of 10%, which is the percentage of crude protein in whole corn reported by Aventis (MRID No. 45025701).

Of the wet-milled fractions, starch contains 0.26% protein, according to the USDA Nutrient Database. Aventis did not detect Cry9C in cornstarch (MRID No. 45025701). Nevertheless, cornstarch-containing foods were included in the dietary intake assessments. Note that, as a worst case, no allowances were made in these numbers for reductions in protein content due to processing, although most corn destined for food products does undergo significant processing such as alkaline soaking, extrusion, etc.

4. The percentage of protein in protein-containing foods that is potentially Cry9C.

For this analysis, 0.0129% of crude protein was assumed to be Cry9C, based on Aventis measurements in whole corn (MRID No. 45025701). This assumption is conservative, as it does not include any losses due to milling, processing or cooking. As mentioned earlier, corn products in the food channel undergo significant processing.

For example, of the 13% of corn that goes to food use (see above), a significant percentage of the amount that is dry-milled is alkaline processed, that is, soaked in a highly basic solution of pH 12 for up to 20 hr before drying and grinding, according to the North American Millers' Association (October 19, 2000, memo from B. Faga), this masa-based product represents 60 million bushels out of a total 220 million bushels processed by the industry, or 27%. Any Cry9C present would be expected to be broken down by this treatment because Cry9C dissolves in highly alkaline solutions (as in the gut of target insects). Indeed Aventis has not found the Cry9C protein in taco shells ("Preliminary Study for Detection of Cry9C Protein in Taco Shells", FIFRA 6(a)(2) report, submitted 10/16/00; "Determination of CBH351 DNA in Taco Shells", FIFRA 6(a)(2) report, submitted 10/16/00). Regardless of these considerations, no adjustment was made for alkaline processing in the analysis.

5. The dietary intake of those foods potentially containing Cry9C.

Consumption data from USDA's 1994-96 Continuing Surveys of Food Intake by Individuals (CFSII) survey were used in the analysis. This is the same database that EPA uses to estimate potential dietary exposures to pesticide residues. All foods with potential to contain protein, and therefore also Cry9C, were included. To determine the daily consumption of foods that potentially contain the Cry9C protein, we queried the CSFII database to calculate the total daily consumption of any foods containing ingredients made from "corn endosperm" (which also includes corn starch) and "corn bran." These are the protein-containing corn fractions.

Daily consumption of foods containing corn protein was determined for the US population and each of the following subpopulations that may be expected to consume high amounts of corn-containing foods: Hispanics, Hispanic children 7-12 years of age, Hispanic children 1-6 years of age, all US children 7-12 years of age, and all US children 1-6 years of age, on both a *per capita* and per user basis. These figures were then multiplied by the exposure factors explained above, in Sections 1-4, to yield the potential daily dietary intake of Cry9C. This approach is consistent with that used for chemical pesticides. These daily intake estimates are presented in Tables 3-6 expressed both as "*per-capita* whole corn consumption" in grams/day and "per-user whole corn consumption" in grams/day.

Notes accompanying the data tables from the CSFII survey caution that intake estimates based on small cell sizes (i.e., small numbers of observations) tend to be less reliable. According to US government policy (Joint Policy on Variance Estimation and Statistical Reporting Standards for the NHANES III and CSFII Reports, Federation of American Societies for Experimental Biology, Life Science Research Office, 1995), statistically unreliable estimates are to be identified ("flagged") in data tables for the information of users. USDA provides a formula for identifying the minimum number of observations needed for an intake estimate above the 75th percentile to be statistically reliable. Based on application of this formula, we have flagged (footnoted) in Tables 3 – 6 any percentile dietary intake estimates which are statistically unreliable, according to federal government policy for use of the survey data.

Tables 3, 4, 7, 8,11 and 12 are based on acres planted in crop year 2000 and consumption of corn endosperm and bran. Tables 5, 6, 9,10, 13, and 14 are based on the year 1999 acres planted and consumption of corn endosperm and bran only. Corn endosperm and bran contain the proteins in corn. No adjustments have been made in these tables for the effects of dry- or wet-milling, processing or cooking on the amounts of the Cry9C protein consumed.

Tables 3-6 show the calculation of the potential amount of the Cry9C protein consumed both per capita and per user in grams based on the following inputs and assumptions:

- The % acres of StarLink™ corn in the US is 0.4% for 2000, and 0.3% for 1999, as explained above.
- The % acres StarLink™ corn theoretically in food channels is explained above.
- 10% is the maximum amount of crude protein found in analyses of whole corn (MRID No. 45025701).
- 0.0129% is the amount of the Cry9C protein found in analyses of whole corn (MRID No. 45025701).
- The per-capita and per-user whole corn consumption in grams/day from the USDA CSFII 1994-1996 data.

The amounts of the Cry9C protein consumed per-capita or per-user were calculated by multiplying from left to right across the table. For example, in Table 3, the "amount Cry9C consumed per capita" is obtained by multiplying 0.4% "acres StarLink™ corn in US" times 12% "acres StarLink™ corn theoretically in food channels" times 10% "crude protein in whole corn" times 0.0129% "Cry9C in whole corn" times 62.3 "per capita whole corn consumption (per day)," resulting in 0.0000004 grams.

The amounts of Cry9C protein potentially consumed, in both the 1999 and 2000 "worst case" scenarios (assuming 50% of StarLink corn) are listed below for those subpopulations at the 99.9th percentile with the highest potential consumption "per user":

1999 (See Table 6)		
Hispanic population	99.9th percentile	6.4 μg
All US Children, 7-12 years	99.9th percentile	6.4 μg
2000 (See Table 4)		
Hispanic population	99.9th percentile	8.5 μg
All US Children, 7-12 years	99.9th percentile	8.6 μg

B. Comparison of the Maximum Estimated Intake of Cry9C Protein/Person/Day to Peanut Allergen in Average Serving Size of Peanut Butter

Based upon the average serving size of peanuts, in the form of peanut butter, an individual would consume 32 g of peanuts, of which 8 g/serving is peanut protein (Yunginger, J.W. 1997; Table 1). Of that 8 g of peanut butter protein, the two major peanut allergens (Ara h1 and Ara h2) comprise approximately 1.3 g. Therefore, 1.3 g of these peanut allergens per serving of peanut butter may be considered to represent an established, ongoing level of exposure among the US population of peanut butter consumers. At this established level, the prevalence of peanut allergy in the US is 1.5 million people (Li et al., 2000); this corresponds to about 0.5% of the population.

For purposes of this safety assessment, we estimated potential intakes of the Cry9C protein to evaluate a “Margin of Exposure (MOE)”. We defined MOE by comparing the potential dietary exposure to the Cry9C protein to existing levels of the potent food allergens in the peanut known to be associated with a quantified level of sensitization in the US population. This approach is presented here and in Tables 7-14.

The ratios or MOEs of potential dietary intake of Cry9C per day to the level of peanut allergen in a single serving of peanut butter, are presented in Tables 7 – 10. Table 7 uses the potential Cry9C intakes from Table 3. Table 8 uses the potential Cry9C intakes from Table 4, and so forth.

In contrast to the level of peanut allergen in a single serving of peanut butter, 1.3 g, the maximum level of the Cry9C protein that would potentially be consumed in the year 2000 by the 99.9th percentile corn consumers in the US population is 0.0000086 g/person/day for All US Children, 7-12 years. (See Table 4.) The comparable 1999 number is slightly less (0.0000064 g/person/day. (See Table 6.) The potential dietary exposure to Cry9C protein per day therefore is more than 151,907 times less than the amount of peanut allergens in an average size serving of peanut butter. (See Table 8.) Given that peanut allergens represent arguably the most potent human food allergens, and that the ongoing level of peanut allergens corresponds to a low prevalence of sensitization in the US population (0.5% as discussed previously), it is reasonable to conclude that the likelihood of sensitization associated with the Cry9C protein in StarLink corn is extremely low.

In contrast to the level of peanut allergen in a single serving of peanut butter, 1.3 g, the maximum consumption of peanut butter per day, from the CSFII data, is 186.4 g (US population,99.9th percentile). Of this, 46.6 g is peanut protein. Of this 46.6 g, the two major peanut allergens, Ara h1 and Ara h2, comprise 7.6 g. This represents the total potential daily exposure to peanut allergens from peanut butter, at the 99.9th percentile. The maximum level of the Cry9C protein that would potentially be consumed in the year 2000 by the 99.9th percentile corn consumers in the US population is 0.0000086 g/person/day for All US Children, 7-12 years. (See Table 4.) The comparable 1999 number is slightly less (0.0000064 g/person/day). (See Table 6.) The potential dietary exposure to Cry9C protein per day therefore is more than 880,000 less than the amount of peanut allergens in the maximum consumption of peanut butter per day. (See Tables 12 and 14.)

A weight of evidence analysis of available data and information, reinforced by Drs. Taylor and Hefle of the Food Allergy and Resource Program at the University of Nebraska, strongly supports the conclusion that Cry9C protein is not likely to be an allergen. However, the analysis discussed above demonstrates that even if the Cry9C protein were an allergen, the potential dietary exposure to Cry9C is so low that sensitization in the population is highly unlikely. Significant MOEs exist.

C. Comparison of Potential Dietary Exposure to Cry9C and Dose of Peanut Allergens Eliciting Responses in Already-Sensitized Individuals

In the most conservative approach to safety assessment of the Cry9C protein, the reasonable worst case dietary exposure to the Cry9C protein per day is compared to the amount of peanut allergen required to elicit a clinical response in peanut sensitized patients. Recall that consistently higher levels of allergens are required to cause sensitization relative to the amount of allergen required to elicit an allergic reaction in already sensitized individuals.

To assess the amount of protein which is required to elicit a response in already sensitized peanut allergic individuals, a quantitative study using a double blind placebo controlled food challenge approach (DBPCFC) was conducted (Hourihane et al., 1997). In this study, highly peanut allergic patients were challenged with peanut protein at levels ranging from 10 μg to 50 mg to determine the threshold of response. The most highly allergic individuals showed clinical reactions, noted by a physician, at doses of 2 mg/serving (corresponding to 320 μ of Ara h1 and Ara h2 peanut allergens). All subjects with convincing objective reactions had short-lived subjective (reported by the patient) reactions to doses of crude peanut protein as low as 100 μ, although reactions were mild.

As Tables 4 and 6 illustrate, even using the most conservative scenario of "50% Acres of StarLink corn in US" and the 99.9th percentile corn consumer ("per-user"), despite their statistical unreliability (as previously discussed), and the highest potential level of exposure to the Cry9C protein, 6.4 μg in 1999 (Hispanic or US All Children, 7-12 years) or 8.5 – 8.6 μg in 2000 (for these same subpopulations), and even if one uses a precautionary principle and assumes that the Cry9C protein was as allergenic as the very potent peanut allergens, these worst case potential consumption levels are less than those which resulted in even mild, subjective symptoms reported by patients already sensitize to peanut allergens.

Perhaps more importantly, the worst case maximum potential human dietary intakes (exposures) to the Cry9C protein, 6.4 µg in 1999 and 8.5 to 8.6 µg in 2000, are also well below the level of peanut allergen exposure that led to mild, objective clinical symptoms of allergy reported by the observing physician in peanut sensitized patients.

Because even the worst case exposure of Cry9C protein is below levels that would result in symptoms for those already sensitized to the most potent food allergen, possible dietary exposure to Cry9C protein is protective for the American population which has not been exposed historically and therefore, is not already sensitized to the Cry9C protein. This reasoning echoes that of both Drs. Steven Taylor and Susan Hefle of the Food Allergy Resource and Research Program.

D. Conclusion of the Safety Assessment

The weight of all the data provides strong evidence of the very low probability of allergenicity of Cry9C protein. (See Appendices 2 and 3.) If however, one assumes that the Cry 9C protein has some inherent allergenic potential, based on estimated worst case exposure levels, it is very unlikely that individuals will become sensitized to Cry9C protein. Even if one were to assume that some individuals were, in fact, sensitized, there is little likelihood that there could be a population "at risk" for allergic reactions because estimated exposures are so minimal.

V. CONCLUSIONS

Based on a very conservative assessment of all available information and data, it is clear that Cry9C protein has an extremely low potential of becoming a food allergen. Based on this comprehensive, weight of the evidence analysis of potential risk, it is clear that the presence of Cry9C protein in food meets the "reasonable certainty of no harm" safety standard under the Food Quality Protection Act (FQPA). This conclusion provides strong support for a time-limited exemption from the requirement for a tolerance for Cry9C protein and the DNA required for its expression in StarLink™ corn.

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TABLE 3

ESTIMATES OF POTENTIAL CRY9C INTAKE FOR CROP YEAR 2000: ASSUMING 12% OF STARLINK™ CORN ACRES IN FOOD CHANNELS

Population Group	%Acres StarLink ™ Corn in US[1]	%Acres StarLink ™ Corn Theoretically in Food Channels[2]	% crude protein in whole corn[3]	% Cry9C in whole corn[3]	Per-Capita whole corn consumption (grams/day)[4]	Per-User whole corn consumption (grams/day)[4]	Amount Cry9C consumed per-capita (g)	Amount Cry9C consumed per-user (g)
US Population								
95th percentile	0.4%	12%	10%	0.0129%	62.3	68.8	0.0000004	0.0000004
99th percentile	0.4%	12%	10%	0.0129%	129.1	140.2	0.0000008	0.0000009
99.9th percentile	0.4%	12%	10%	0.0129%	292.7	312.5	0.0000018	0.0000019
All US Children 1-6								
95th percentile	0.4%	12%	10%	0.0129%	40.0	41.6	0.0000002	0.0000003
99th percentile	0.4%	12%	10%	0.0129%	68.0	69.6	0.0000004	0.0000004
99.9th percentile[5]	0.4%	12%	10%	0.0129%	146.4	146.7	0.0000009	0.0000009
All US Children 7-12								
95th percentile	0.4%	12%	10%	0.0129%	61.6	64.9	0.0000004	0.0000004
99th percentile	0.4%	12%	10%	0.0129%	108.9	110.1	0.0000007	0.0000007
99.9th percentile[5]	0.4%	12%	10%	0.0129%	330.7	331.7	0.0000020	0.0000021

[1] Aventis CropScience data

[2] Aventis CropScience data from an on-going survey of growers document that 6% of StarLink hypothetically may enter the food channels. Use of the 12% value is conservative.

[3] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.

[4] Based on estimates from USDA CSFII 1994-1996 data

[5] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 3 (CONT'D)

Population Group	%Acres StarLink™ Corn in US[6]	%Acres StarLink™ Corn Theoretically in Food Channels[7]	% crude protein in whole corn[8]	% Cry9C in whole corn[3]	Per-Capita whole corn consumption (grams/day)[9]	Per-User whole corn consumption (grams/day)[4]	Amount Cry9C consumed per-capita (g)	Amount Cry9C consumed per-user (g)
Hispanic Population								
95th percentile	0.4%	12%	10%	0.0129%	87.7	98.8	0.0000005	0.0000006
99th percentile	0.4%	12%	10%	0.0129%	172.3	179.2	0.0000011	0.0000011
99.9th percentile[5]	0.4%	12%	10%	0.0129%	317.2	328.6	0.0000020	0.0000020
Hispanic Children 1-6								
95th percentile	0.4%	12%	10%	0.0129%	46.5	48.7	0.0000003	0.0000003
99th percentile[5]	0.4%	12%	10%	0.0129%	79.1	19.5	0.0000005	0.0000001
99.9th percentile[5]	0.4%	12%	10%	0.0129%	152.5	315.5	0.0000009	0.0000020
Hispanic Children 7-12								
95th percentile	0.4%	12%	10%	0.0129%	90.4	91.3	0.0000006	0.0000006
99th percentile[5]	0.4%	12%	10%	0.0129%	122.4	122.9	0.0000008	0.0000008
99.9th percentile[5]	0.4%	12%	10%	0.0129%	286.8	286.9	0.0000018	0.0000018

[6] Aventis CropScience data
[7] Aventis CropScience data from an on-going survey of growers document that 6% of StarLink hypothetically may enter the food channels. Use of the 12% value is conservative.
[8] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.
[9] Based on estimates from USDA CSFII 1994-1996 data

TABLE 4

ESTIMATES OF POTENTIAL CRY9C INTAKE FOR CROP YEAR 2000: ASSUMING 50% OF STARLINK™ CORN ACRES IN FOOD CHANNELS

Population Group	% Acres StarLink™ Corn in US[1]	%Acres StarLink™ Corn Theoretically in Food Channels[2]	% crude protein in whole corn[3]	% Cry9C in whole corn[3]	Per-Capita whole corn consumption (grams/day)[4]	Per-User whole corn consumption (grams/day)[4]	Worst Case Cry9C consumed per-capita (g)	Worst Case Cry9C consumed per-user (g)
US Population								
95th percentile	0.4%	50%	10%	0.0129%	62.3	68.8	0.0000016	0.0000018
99th percentile	0.4%	50%	10%	0.0129%	129.1	140.2	0.0000033	0.0000036
99.9th percentile	0.4%	50%	10%	0.0129%	292.7	312.5	0.0000076	0.0000081
All US Children 1-6								
95th percentile	0.4%	50%	10%	0.0129%	40	41.6	0.0000010	0.0000011
99th percentile	0.4%	50%	10%	0.0129%	68	69.6	0.0000018	0.0000018
99.9th percentile[5]	0.4%	50%	10%	0.0129%	146.4	146.7	0.0000038	0.0000038
All US Children 7-12								
95th percentile	0.4%	50%	10%	0.0129%	61.6	64.9	0.0000016	0.0000017
99th percentile	0.4%	50%	10%	0.0129%	108.9	110.1	0.0000028	0.0000028
99.9th percentile[5]	0.4%	50%	10%	0.0129%	330.7	331.7	0.0000085	0.0000086
Hispanic Population								
95th percentile	0.4%	50%	10%	0.0129%	87.7	98.8	0.0000023	0.0000025
99th percentile	0.4%	50%	10%	0.0129%	172.3	179.2	0.0000044	0.0000046
99.9th percentile[5]	0.4%	50%	10%	0.0129%	317.2	328.6	0.0000082	0.0000085

[1] Aventis CropScience data

[2] This assumes that yellow corn has an equal chance of being used for feed or food, although available USDA statistics indicate that most goes to nonfood channels. See Section E 2b,Potential Exposure to Cry9C

[3] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.

[4] Based on estimates from USDA CSFII 1994-1996 data

[5] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 4 (CONT'D)

Population Group	% Acres StarLink™ Corn in US[6]	%Acres StarLink™ Corn Theoretically in Food Channels[7]	% crude protein in whole corn[8]	% Cry9C in whole corn[8]	Per-Capita whole corn consumption (grams/day)[9]	Per-User whole corn consumption (grams/day)[9]	Worst Case Cry9C consumed per-capita (g)	Worst Case Cry9C consumed per-user (g)
Hispanic Children 1-6								
95th percentile	0.4%	50%	10%	0.0129%	46.5	48.7	0.0000012	0.0000013
99th percentile[5]	0.4%	50%	10%	0.0129%	79.1	79.5	0.0000020	0.0000021
99.9th percentile[5]	0.4%	50%	10%	0.0129%	152.5	315.5	0.0000039	0.0000081
Hispanic Children 7-12								
95th percentile	0.4%	50%	10%	0.0129%	90.4	91.3	0.0000023	0.0000024
99th percentile[5]	0.4%	50%	10%	0.0129%	122.4	122.9	0.0000032	0.0000032
99.9th percentile[5]	0.4%	50%	10%	0.0129%	286.8	286.9	0.0000074	0.0000074

[6] Aventis CropScience data
[7] This assumes that yellow corn has an equal chance of being used for feed or food, although available USDA statistics indicate that most goes to nonfood channels. See Section E 2b,Potential Exposure to Cry9C
[8] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.
[9] Based on estimates from USDA CSFII 1994-1996 data

TABLE 5

ESTIMATES OF POTENTIAL CRY9C INTAKE FOR CROP YEAR 1999: ASSUMING 13% OF STARLINK™ CORN ACRES IN FOOD CHANNELS

Population Group	% Acres StarLink™ Corn in US	%Acres StarLink™ Corn Theoretically in Food Channels	% crude protein in whole corn	% Cry9C in whole corn	Per-Capita corn consumption (grams/day)	Per-User corn consumption (grams/day)	Worst Case Cry9C consumed Per-capita (g)	Worst Case Cry9C consumed per-user (g)
US Population								
95th percentile	0.3%	13%	10%	0.0129%	62.3	68.8	0.0000003	0.0000003
99th percentile	0.3%	13%	10%	0.0129%	129.1	140.2	0.0000006	0.0000007
99.9th percentile	0.3%	13%	10%	0.0129%	292.7	312.5	0.0000015	0.0000016
All US Children 1-6								
95th percentile	0.3%	13%	10%	0.0129%	40	41.6	0.0000002	0.0000002
99th percentile	0.3%	13%	10%	0.0129%	68	69.6	0.0000003	0.0000004
99.9th percentile[1]	0.3%	13%	10%	0.0129%	146.4	146.7	0.0000007	0.0000007
All US Children 7-12								
95th percentile	0.3%	13%	10%	0.0129%	61.6	64.9	0.0000003	0.0000003
99th percentile	0.3%	13%	10%	0.0129%	108.9	110.1	0.0000005	0.0000006
99.9th percentile[1]	0.3%	13%	10%	0.0129%	330.7	331.7	0.0000017	0.0000017
Hispanic Population								
95th percentile	0.3%	13%	10%	0.0129%	87.7	98.8	0.0000004	0.0000005
99th percentile	0.3%	13%	10%	0.0129%	172.3	179.2	0.0000009	0.0000009
99.9th percentile[1]	0.3%	13%	10%	0.0129%	317.2	328.6	0.0000016	0.0000017

[1] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 5 (CONT'D)

Population Group	% Acres StarLink™ Corn in US	%Acres StarLink™ Corn Theoretically in Food Channels	% crude protein in whole corn	% Cry9C in whole corn	Per-Capita corn consumption (grams/day)	Per-User corn consumption (grams/day)	Worst Case Cry9C consumed Per-capita (g)	Worst Case Cry9C consumed per-user (g)
Hispanic Children 1-6								
95th percentile	0.3%	13%	10%	0.0129%	46.5	48.7	0.0000002	0.0000002
99th percentile[1]	0.3%	13%	10%	0.0129%	79.1	79.5	0.0000004	0.0000004
99.9th percentile[1]	0.3%	13%	10%	0.0129%	152.5	315.5	0.0000008	0.0000016
Hispanic Children 7-12								
95th percentile	0.3%	13%	10%	0.0129%	90.4	91.3	0.0000005	0.0000005
99th percentile[1]	0.3%	13%	10%	0.0129%	122.4	122.9	0.0000006	0.0000006
99.9th percentile[1]	0.3%	13%	10%	0.0129%	286.8	286.9	0.0000014	0.0000014

[1] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 6

ESTIMATES OF POTENTIAL CRY9C INTAKE FOR CROP YEAR 1999: ASSUMING 50% OF STARLINK™ CORN ACRES IN FOOD CHANNELS

Population Group	% Acres StarLink™ Corn in US[1]	%Acres StarLink™ Corn Theoretically in Food Channels[2]	% crude protein in whole corn[3]	% Cry9C in whole corn[3]	Per-Capita corn consumption (grams/day)	Per-User corn consumption (grams/day)	Worst Case Cry9C consumed Per-capita (g)	Worst Case Cry9C consumed per-user (g)
US Population								
95th percentile	0.3%	50%	10%	0.0129%	62.3	68.8	0.0000012	0.0000013
99th percentile	0.3%	50%	10%	0.0129%	129.1	140.2	0.0000025	0.0000027
99.9th percentile	0.3%	50%	10%	0.0129%	292.7	312.5	0.0000057	0.0000060
All US Children 1 to 6 years								
95th percentile	0.3%	50%	10%	0.0129%	40	41.6	0.0000008	0.0000008
99th percentile	0.3%	50%	10%	0.0129%	68	69.6	0.0000013	0.0000013
99.9th percentile[4]	0.3%	50%	10%	0.0129%	146.4	146.7	0.0000028	0.0000028
All US Children 7-12								
95th percentile	0.3%	50%	10%	0.0129%	61.6	64.9	0.0000012	0.0000013
99th percentile	0.3%	50%	10%	0.0129%	108.9	110.1	0.0000021	0.0000021
99.9th percentile[4]	0.3%	50%	10%	0.0129%	330.7	331.7	0.0000064	0.0000064
Hispanic Population								
95th percentile	0.3%	50%	10%	0.0129%	87.7	98.8	0.0000017	0.0000019
99th percentile	0.3%	50%	10%	0.0129%	172.3	179.2	0.0000033	0.0000035
99.9th percentile[4]	0.3%	50%	10%	0.0129%	317.2	328.6	0.0000061	0.0000064

[1] Aventis CropScience data
[2] This assumes that yellow corn has an equal chance of being used for feed or food, although USDA statistics indicate that most goes to nonfood channels. See Section E
2b, Potential Exposure to Cry9C
[3] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.
[4] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 6 (CONT'D)

Population Group	% Acres StarLink™ Corn in US[5]	%Acres StarLink™ Corn Theoretically in Food Channels[6]	% crude protein in whole corn[7]	% Cry9C in whole corn[7]	Per-Capita corn consumption (grams/day)	Per-User corn consumption (grams/day)	Worst Case Cry9C consumed Per-capita (g)	Worst Case Cry9C consumed per-user (g)
Hispanic Children 1-6								
95th percentile	0.3%	50%	10%	0.0129%	46.5	48.7	0.0000009	0.0000009
99th percentile[8]	0.3%	50%	10%	0.0129%	79.1	79.5	0.0000015	0.0000015
99.9th percentile[8]	0.3%	50%	10%	0.0129%	152.5	315.5	0.0000030	0.0000061
Hispanic Children 7 to 12 years								
95th percentile	0.3%	50%	10%	0.0129%	90.4	91.3	0.0000017	0.0000018
99th percentile[8]	0.3%	50%	10%	0.0129%	122.4	122.9	0.0000024	0.0000024
99.9th percentile[8]	0.3%	50%	10%	0.0129%	286.8	286.9	0.0000055	0.0000056

[5] Aventis CropScience data
[6] This assumes that yellow corn has an equal chance of being used for feed or food, although USDA statistics indicate that most goes to nonfood channels. See Section E
2b, Potential Exposure to Cry9C
[7] Aventis CropScience data, Ray Shilito author. Data submitted to the Agency 10/24/00.
[8] According to Federal Government policy and procedures, this percentile estimate is not statistically reliable. See text.

TABLE 7

COMPARISON OF DAILY CRY9C INTAKE (YEAR 2000, 12% STARLINK™ CORN) AND PEANUT ALLERGENS IN ONE SERVING PEANUT BUTTER SAFETY

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	1.3 grams	0.0000004	0.0000004	3,369,957	3,051,574
99th percentile	1.3 grams	0.0000008	0.0000009	1,626,246	1,497,492
99.9th percentile	1.3 grams	0.0000018	0.0000019	717,282	671,835
All US Children 1 to 6 years					
95th percentile	1.3 grams	0.0000002	0.0000003	5,248,708	5,046,835
99th percentile	1.3 grams	0.0000004	0.0000004	3,087,475	3,016,499
99.9th percentile	1.3 grams	0.0000009	0.0000009	1,434,073	1,431,141
All US Children 7 to 12 years					
95th percentile	1.3 grams	0.0000004	0.0000004	3,408,252	3,234,951
99th percentile	1.3 grams	0.0000007	0.0000007	1,927,900	1,906,888
99.9th percentile	1.3 grams	0.0000020	0.0000021	634,860	632,946
Hispanics					
95th percentile	1.3 grams	0.0000005	0.0000006	2,393,938	2,124,983
99th percentile	1.3 grams	0.0000011	0.0000011	1,218,504	1,171,587
99.9th percentile	1.3 grams	0.0000020	0.0000020	661,880	638,918

[1] "Margin of Exposure" for purposes of this assessment is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 7 (CONT'D)

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	1.3 grams	0.0000003	0.0000003	4,515,018	4,311,054
99th percentile	1.3 grams	0.0000005	0.0000005	2,654,214	2,640,859
99.9th percentile	1.3 grams	0.0000009	0.0000020	1,376,710	665,446
Hispanic Children 7 to 12 years					
95th percentile	1.3 grams	0.0000006	0.0000006	2,322,437	2,299,543
99th percentile	1.3 grams	0.0000008	0.0000008	1,715,264	1,708,286
99.9th percentile	1.3 grams	0.0000018	0.0000018	732,037	731,782

[2] "Margin of Exposure" for purposes of this assessment is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 8

COMPARISON OF DAILY CRY9C INTAKE (YEAR 2000, 50% STARLINK™ CORN) AND PEANUT ALLERGENS IN ONE SERVING PEANUT BUTTER

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	1.3 grams	0.0000016	0.0000018	808,790	732,378
99th percentile	1.3 grams	0.0000033	0.0000036	390,299	359,398
99.9th percentile	1.3 grams	0.0000076	0.0000081	172,148	161,240
All US Children 1 to 6 years					
95th percentile	1.3 grams	0.0000010	0.0000011	1,259,690	1,211,240
99th percentile	1.3 grams	0.0000018	0.0000018	740,994	723,960
99.9th percentile	1.3 grams	0.0000038	0.0000038	344,178	343,474
All US Children 7 to 12 years					
95th percentile	1.3 grams	0.0000016	0.0000017	817,980	776,388
99th percentile	1.3 grams	0.0000028	0.0000028	462,696	457,653
99.9th percentile	1.3 grams	0.0000085	0.0000086	152,366	151,907
Hispanics					
95th percentile	1.3 grams	0.0000023	0.0000025	574,545	509,996
99th percentile	1.3 grams	0.0000044	0.0000046	292,441	281,181
99.9th percentile	1.3 grams	0.0000082	0.0000085	158,851	153,340

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 8 (CONT’D)

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	“Margin of Exposure”[2] per-capita	“Margin of Exposure” per-user
Hispanic Children 1 to 6 years					
95th percentile	1.3 grams	0.0000012	0.0000013	1,083,604	1,034,653
99th percentile	1.3 grams	0.0000020	0.0000021	637,011	633,806
99.9th percentile	1.3 grams	0.0000039	0.0000081	330,410	159,707
Hispanic Children 7 to 12 years					
95th percentile	1.3 grams	0.0000023	0.0000024	557,385	551,890
99th percentile	1.3 grams	0.0000032	0.0000032	411,663	409,989
99.9th percentile	1.3 grams	0.0000074	0.0000074	175,689	175,628

[2] “Margin of Exposure” is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 9

COMPARISON OF DAILY CRY9C INTAKE (YEAR 1999, 13% STARLINK™ CORN) AND PEANUT ALLERGENS IN ONE SERVING PEANUT BUTTER

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	1.3 grams	0.0000003	0.0000003	4,147,639	3,755,784
99th percentile	1.3 grams	0.0000006	0.0000007	2,001,533	1,843,067
99.9th percentile	1.3 grams	0.0000015	0.0000016	882,808	826,873
All US Children 1 to 6 years					
95th percentile	1.3 grams	0.0000002	0.0000002	6,459,948	6,211,489
99th percentile	1.3 grams	0.0000003	0.0000004	3,799,970	3,712,614
99.9th percentile	1.3 grams	0.0000007	0.0000007	1,765,013	1,761,404
All US Children 7 to 12 years					
95th percentile	1.3 grams	0.0000003	0.0000003	4,194,772	3,981,478
99th percentile	1.3 grams	0.0000005	0.0000006	2,372,800	2,346,939
99.9th percentile	1.3 grams	0.0000017	0.0000017	781,367	779,011
Hispanics					
95th percentile	1.3 grams	0.0000004	0.0000005	2,946,385	2,615,364
99th percentile	1.3 grams	0.0000009	0.0000009	1,499,698	1,441,953
99.9th percentile	1.3 grams	0.0000016	0.0000017	814,621	786,360

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 9 (CONT'D)

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	1.3 grams	0.0000002	0.0000002	5,556,945	5,305,912
99th percentile	1.3 grams	0.0000004	0.0000004	3,266,725	3,250,288
99.9th percentile	1.3 grams	0.0000008	0.0000016	1,694,413	819,011
Hispanic Children 7 to 12 years					
95th percentile	1.3 grams	0.0000005	0.0000005	2,858,384	2,830,207
99th percentile	1.3 grams	0.0000006	0.0000006	2,111,094	2,102,506
99.9th percentile	1.3 grams	0.0000014	0.0000014	900,969	900,655

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 10

COMPARISON OF DAILY CRY9C INTAKE (YEAR 1999, 50% STARLINK™ CORN) AND PEANUT ALLERGENS IN ONE SERVING PEANUT BUTTER

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	1.3 grams	0.0000012	0.0000013	1,078,386	976,504
99th percentile	1.3 grams	0.0000025	0.0000027	520,399	479,197
99.9th percentile	1.3 grams	0.0000057	0.0000060	229,530	214,987
All US Children 1 to 6 years					
95th percentile	1.3 grams	0.0000008	0.0000008	1,679,587	1,614,987
99th percentile	1.3 grams	0.0000013	0.0000013	987,992	965,280
99.9th percentile	1.3 grams	0.0000028	0.0000028	458,903	457,965
All US Children 7 to 12 years					
95th percentile	1.3 grams	0.0000012	0.0000013	1,090,641	1,035,184
99th percentile	1.3 grams	0.0000021	0.0000021	616,928	610,204
99.9th percentile	1.3 grams	0.0000064	0.0000064	203,155	202,543
Hispanics					
95th percentile	1.3 grams	0.0000017	0.0000019	766,060	679,995
99th percentile	1.3 grams	0.0000033	0.0000035	389,921	374,908
99.9th percentile	1.3 grams	0.0000061	0.0000064	211,802	204,454

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 10 (CONT'D)

Population Group	Peanut allergen in average 32g serving	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	1.3 grams	0.0000009	0.0000009	1,444,806	1,379,537
99th percentile	1.3 grams	0.0000015	0.0000015	849,348	845,075
99.9th percentile	1.3 grams	0.0000030	0.0000061	440,547	212,943
Hispanic Children 7 to 12 years					
95th percentile	1.3 grams	0.0000017	0.0000018	743,180	735,854
99th percentile	1.3 grams	0.0000024	0.0000024	548,884	546,651
99.9th percentile	1.3 grams	0.0000055	0.0000056	234,252	234,170

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 11

COMPARISON OF DAILY CRY9C INTAKE (YEAR 2000, 12% STARLINK™ CORN) AND PEANUT ALLERGENS IN DAILY PEANUT BUTTER CONSUMPTION

Population Group	Maximum Peanut allergen in Peanut Butter consumed/day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	7.6 grams	0.0000004	0.0000004	19,701,287	17,839,974
99th percentile	7.6 grams	0.0000008	0.0000009	9,507,283	8,754,566
99.9th percentile	7.6 grams	0.0000018	0.0000019	4,193,339	3,927,649
All US Children 1 to 6 years					
95th percentile	7.6 grams	0.0000002	0.0000003	30,684,755	29,504,572
99th percentile	7.6 grams	0.0000004	0.0000004	18,049,856	17,634,916
99.9th percentile	7.6 grams	0.0000009	0.0000009	8,383,813	8,366,668
All US Children 7 to 12 years					
95th percentile	7.6 grams	0.0000004	0.0000004	19,925,165	18,912,021
99th percentile	7.6 grams	0.0000007	0.0000007	11,270,801	11,147,958
99.9th percentile	7.6 grams	0.0000020	0.0000021	3,711,491	3,700,302
Hispanics					
95th percentile	7.6 grams	0.0000005	0.0000006	13,995,327	12,422,978
99th percentile	7.6 grams	0.0000011	0.0000011	7,123,565	6,849,276
99.9th percentile	7.6 grams	0.0000020	0.0000020	3,869,452	3,735,211

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 11 (CONT'D)

Population Group	Maximum Peanut allergen in Peanut Butter consumed/day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	7.6 grams	0.0000003	0.0000003	26,395,488	25,203,084
99th percentile	7.6 grams	0.0000005	0.0000005	15,516,943	15,438,870
99.9th percentile	7.6 grams	0.0000009	0.0000020	8,048,460	3,890,302
Hispanic Children 7 to 12 years					
95th percentile	7.6 grams	0.0000006	0.0000006	13,577,325	13,443,485
99th percentile	7.6 grams	0.0000008	0.0000008	10,027,698	9,986,901
99.9th percentile	7.6 grams	0.0000018	0.0000018	4,279,603	4,278,111

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 12

COMPARISON OF DAILY CRY9C INTAKE (YEAR 2000, 50% STARLINK™ CORN) AND PEANUT ALLERGENS IN DAILY PEANUT BUTTER CONSUMPTION

Population Group	Maximum Peanut allergen in Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	7.6 grams	0.0000016	0.0000018	4,728,309	4,281,594
99th percentile	7.6 grams	0.0000033	0.0000036	2,281,748	2,101,096
99.9th percentile	7.6 grams	0.0000076	0.0000081	1,006,401	942,636
All US Children 1 to 6 years					
95th percentile	7.6 grams	0.0000010	0.0000011	7,364,341	7,081,097
99th percentile	7.6 grams	0.0000018	0.0000018	4,331,965	4,232,380
99.9th percentile	7.6 grams	0.0000038	0.0000038	2,012,115	2,008,000
All US Children 7 to 12 years					
95th percentile	7.6 grams	0.0000016	0.0000017	4,782,040	4,538,885
99th percentile	7.6 grams	0.0000028	0.0000028	2,704,992	2,675,510
99.9th percentile	7.6 grams	0.0000085	0.0000086	890,758	888,072
Hispanics					
95th percentile	7.6 grams	0.0000023	0.0000025	3,358,878	2,981,515
99th percentile	7.6 grams	0.0000044	0.0000046	1,709,656	1,643,826
99.9th percentile	7.6 grams	0.0000082	0.0000085	928,668	896,451

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 12 (CONT'D)

Population Group	Maximum Peanut allergen in Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	7.6 grams	0.0000012	0.0000013	6,334,917	6,048,740
99th percentile	7.6 grams	0.0000020	0.0000021	3,724,066	3,705,329
99.9th percentile	7.6 grams	0.0000039	0.0000081	1,931,630	933,672
Hispanic Children 7 to 12 years					
95th percentile	7.6 grams	0.0000023	0.0000024	3,258,558	3,226,436
99th percentile	7.6 grams	0.0000032	0.0000032	2,406,647	2,396,856
99.9th percentile	7.6 grams	0.0000074	0.0000074	1,027,105	1,026,747

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 13

COMPARISON OF DAILY CRY9C INTAKE (YEAR 1999, 13% STARLINK™ CORN) AND PEANUT ALLERGENS IN DAILY PEANUT BUTTER CONSUMPTION

Population Group	Maximum Peanut allergen from Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	7.6 grams	0.0000003	0.0000003	24,247,738	21,956,891
99th percentile	7.6 grams	0.0000006	0.0000007	11,701,271	10,774,851
99.9th percentile	7.6 grams	0.0000015	0.0000016	5,161,032	4,834,029
All US Children 1 to 6 years					
95th percentile	7.6 grams	0.0000002	0.0000002	37,765,852	36,313,319
99th percentile	7.6 grams	0.0000003	0.0000004	22,215,207	21,704,512
99.9th percentile	7.6 grams	0.0000007	0.0000007	10,318,539	10,297,437
All US Children 7 to 12 years					
95th percentile	7.6 grams	0.0000003	0.0000003	24,523,280	23,276,334
99th percentile	7.6 grams	0.0000005	0.0000006	13,871,755	13,720,564
99.9th percentile	7.6 grams	0.0000017	0.0000017	4,567,989	4,554,218
Hispanics					
95th percentile	7.6 grams	0.0000004	0.0000005	17,225,018	15,289,819
99th percentile	7.6 grams	0.0000009	0.0000009	8,767,464	8,429,878
99.9th percentile	7.6 grams	0.0000016	0.0000017	4,762,402	4,597,182

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 13 (CONT'D)

Population Group	Maximum Peanut allergen from Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	7.6 grams	0.0000002	0.0000002	32,486,754	31,019,180
99th percentile	7.6 grams	0.0000004	0.0000004	19,097,776	19,001,686
99.9th percentile	7.6 grams	0.0000008	0.0000016	9,905,797	4,788,064
Hispanic Children 7 to 12 years					
95th percentile	7.6 grams	0.0000005	0.0000005	16,710,554	16,545,828
99th percentile	7.6 grams	0.0000006	0.0000006	12,341,782	12,291,571
99.9th percentile	7.6 grams	0.0000014	0.0000014	5,267,204	5,265,368

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 14

COMPARISON OF DAILY CRY9C INTAKE (YEAR 1999, 50% STARLINK™ CORN) AND PEANUT ALLERGENS IN DAILY PEANUT BUTTER CONSUMPTION

Population Group	Maximum Peanut allergen from Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[1] per-capita	"Margin of Exposure" per-user
US Population					
95th percentile	7.6 grams	0.0000012	0.0000013	6,304,412	5,708,792
99th percentile	7.6 grams	0.0000025	0.0000027	3,042,330	2,801,461
99.9th percentile	7.6 grams	0.0000057	0.0000060	1,341,868	1,256,848
All US Children 1 to 6 years					
95th percentile	7.6 grams	0.0000008	0.0000008	9,819,121	9,441,463
99th percentile	7.6 grams	0.0000013	0.0000013	5,775,954	5,643,173
99.9th percentile	7.6 grams	0.0000028	0.0000028	2,682,820	2,677,334
All US Children 7 to 12 years					
95th percentile	7.6 grams	0.0000012	0.0000013	6,376,053	6,051,847
99th percentile	7.6 grams	0.0000021	0.0000021	3,606,656	3,567,347
99.9th percentile	7.6 grams	0.0000064	0.0000064	1,187,677	1,184,097
Hispanics					
95th percentile	7.6 grams	0.0000017	0.0000019	4,478,505	3,975,353
99th percentile	7.6 grams	0.0000033	0.0000035	2,279,541	2,191,768
99.9th percentile	7.6 grams	0.0000061	0.0000064	1,238,225	1,195,267

[1] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

TABLE 14 (CONT'D)

Population Group	Maximum Peanut allergen from Peanut Butter consumed per day	Maximum Daily Cry9C consumed per-capita (grams)	Maximum Daily Cry9C consumed per-user (grams)	"Margin of Exposure"[2] per-capita	"Margin of Exposure" per-user
Hispanic Children 1 to 6 years					
95th percentile	7.6 grams	0.0000009	0.0000009	8,446,556	8,064,987
99th percentile	7.6 grams	0.0000015	0.0000015	4,965,422	4,940,438
99.9th percentile	7.6 grams	0.0000030	0.0000061	2,575,507	1,244,897
Hispanic Children 7 to 12 years					
95th percentile	7.6 grams	0.0000017	0.0000018	4,344,744	4,301,915
99th percentile	7.6 grams	0.0000024	0.0000024	3,208,863	3,195,808
99.9th percentile	7.6 grams	0.0000055	0.0000056	1,381,818	1,357,143

[2] "Margin of Exposure" is defined as the amount of peanut allergen/amount of Cry9C. The comparison is relating potential Cry9C exposure to level of allergen in a food known to be associated with quantified level of sensitization in the US population.

APPENDIX 1

CORN HANDLING AND GRAIN HANDLING DISCUSSION

APPENDIX 1

CORN HANDLING AND GRAIN PROCESSING DISCUSSION*

Whole Corn Handling Operations from Farm to Elevator

Virtually all farmers harvest corn with a combine with an attached corn header, and transfer the harvested grain from the combine to a truck to deliver either to on-farm storage or a commercial grain elevator. Farm trucks typically hold 200 to 800 bushels with the average size about 400 bushels.

When the grain is delivered to a local elevator, the grain is dumped into a pit covered by an iron grate (which removes large foreign objects). The pit may be able to hold one or more truck loads of grain at a given time. From the pit, the grain is normally conveyed (via belt or drag conveyor) to a bucket elevator which elevates the grain to the top of grain storage bins where it is dropped to the bottom of the bin, or onto other grain. Bin sizes at elevators generally range from 10,000 bushels to 1,000,000 bushels, with an average of 70,000 to 80,000 bushels

When the grain is loaded out of the elevator, it is drawn from the bottom of the bin. The grain flows out of the bin onto a belt or a drag conveyer, and then elevated to again be dumped into a truck, barge or railcar for transshipment to a feeding operation, to a terminal elevator (for additional storage), to a grain processor or to an export location.

From the time of receipt through load-out, there is a continuous blending and commingling of the corn received from individual farmers. The farm truck often carries corn taken from different fields on the farm. Truckloads are dumped successively on top of each other, but the necessary handling, conditioning and management of elevator storage space ensures that individual truckloads lose their identity. Corn that is dried is handled in a different stream through the dryer prior to going to a bin, adding to the commingling process. At some elevators, multiple truck dump pits are combined into one grain stream entering storage. At all facilities, the need to move grain from bin to bin for conditioning of the grain and to open up additional empty bins forces the contents of multiple bins to be commingled into one during handling. Further commingling occurs during load-out as the elevator manager often draws grain from multiple bins to intentionally blend the grain to meet quality specifications for different customers.

As grain is dropped from the top of storage bins at the elevator, the grain forms an inverted conical shape, as the grain enters at the center and flows out to the sides of the bin. There is a "layering" effect of the grain entering the bin. When the grain is drawn from the bottom of the bin, a different flow pattern develops. The grain flowing out will form a "core" in the center. The center portion of the grain bin flows out first, then a cone develops, with the upper portions of the grain flowing out toward the early part of the removal process. As the bin empties, the grain at the sides of the bins starts to flow inward toward the center "core." All the grain deliveries used to fill the bin are commingled in the storage/handling process. The degree of mixing of the grain will depend in part on the point at which the grain entered the bin---near the beginning of the bin-filling process or near the end. The last lot of grain dumped into the bin is likely to have the least amount of commingling in the stream of grain exiting the bin, because the top portion of the grain tends to flow out earlier. Those trucks dumped near the middle of the bin-filling process are commingled most extensively.

If an average farm truck load of 400 bushels of pure StarLink™ corn was delivered to an elevator and placed into a small 10,000 bushel bin, a commingling/dilution of that grain on the order of 3 to 5 times is a conservative expectation, with 3 probably a "worst case" situation. This worst case situation would assume the very minimum number of handlings for drying, conditioning and blending (to meet quality specifications) in the elevator prior to load-out.

Grain Processing at Dry Mills

Grain is delivered from elevators to dry corn mills via trucks or rail cars. Trucks typically haul 1,000 bushels with rail cars holding about 3,500 bushels. The initial receiving process is much like that at the elevator, dumping into a pit and elevating grain into storage bins, which hold the grain until it enters the processing stream.

Most dry corn mills are continuous process (rather than batch). The corn is transferred from the storage bins to a "surge" bin that holds the grain prior to going into a tempering process (where water is added to condition the grain for efficient processing). After tempering, the corn enters the milling process where a series of grinding and sifting operations take place. The germ and the bran are removed from the kernel, and the remaining endosperm portion is reduced to the appropriate size for the product being manufactured. The wide variety of products manufactured includes flaking grits, cereal grits, brewers' grits, corn meal, corn flour, etc.

The various products from milling are transferred into different mill product storage bins depending on intended shipment method. No single bushel goes into any one product bin. The milling of each bushel of corn will create many different particle sizes, each of which goes into a different product bin. From these bins, product may be loaded out in bulk truck or rail or into bags for delivery to a packaging operation or company which may further process or mix the product with other ingredients to produce retail products.

Each handling process into and out of storage, and each processing operation causes the corn and its products to be diluted further. Through storage, tempering, multiple grinding/sifting operations, transfer into product bins, further processing into retail products, there are at least 7-8 distinct points of dilution during the entire voyage from field to end-user.

Because the grain in a milling operation is being continuously mixed through tempering, milling, and handling, the degree of dilution at any one stage is probably much greater than the factor of three, considered to be the "worst case" at the elevator. However, assuming conservatively that there are only seven handling and processing operations, each of which is assumed to dilute the grain by a factor of three, suggests that one truckload of pure StarLink™ corn would be diluted by several orders of magnitude, prior to reaching the consumer.

* Discussion prepared by Betsy Faga, President of the North American Millers Association and Kendall Keith, President of the National Grain and Feed Association

APPENDIX 2

LETTER FROM SUSAN L. HEFLE, PH.D., FOOD ALLERGY RESEARCH AND RESOURCES PROGRAM, UNIVERSITY OF NEBRASKA

APPENDIX 3

WRITTEN STATEMENT BY DR. STEVE L. TAYLOR, FOOD ALLERGY RESEARCH AND RESOURCE PROGRAM, UNIVERSITY OF NEBRASKA