EPA PRELIMINARY EVALUATION OF INFORMATION CONTAINED IN THE OCTOBER 25, 2000 SUBMISSION FROM AVENTIS CROPSCIENCE

EXECUTIVE SUMMARY

The following material constitutes EPA's *Preliminary Evaluation of Information Contained in the October 25, 2000 Submission from Aventis CropScience.* EPA prepared this *"Preliminary Evaluation"* for the FIFRA Scientific Advisory Panel (SAP), an advisory committee of independent, external, expert scientists who provide advice to EPA on scientific issues arising in the context of regulation of pesticide products. This document is part of a larger body of information to be reviewed by the SAP at a public meeting on November 28, 2000. Specifically, the SAP will discuss whether the Cry9C protein produced by a line of genetically modified corn plants, sold commercially under the name "StarLink" by Aventis CropScience USA, LP (Aventis), poses a risk to humans as a potential food allergen. For additional information concerning this meeting refer to EPA's website: www.epa.gov/scipoly/sap and refer to the November 28 date.

Aventis is seeking an exemption from the requirement of a tolerance under the Federal Food, Drug, and Cosmetic Act for the Cry9C protein, and the genetic material necessary to produce it, that may be present in processed food made from StarLink corn grain. On October 25, 2000, Aventis submitted a request to amend its initial petition, to restrict the exemption only to food products made from StarLink corn grain harvested during this or prior years. (Aventis has voluntarily canceled the registration for StarLink, and as a result, there will be no StarLink grain harvest in future years.) Because the requested exemption would apply only to food products made from the 1998, 1999, and 2000 StarLink corn crops, Aventis proposed that the exemption would be time-limited, i.e. only for the four years that would be needed for the food items to clear the channels of trade. The Aventis submission also included new information in support of the requested amendment. Aventis contends this information shows that: 1) the Cry9C protein and DNA are neither toxic nor human food allergens; 2) exposure to the Cry9C protein is so low that it is unlikely to have caused sensitization; and 3) exposure to the Cry9C protein is so low that it is not likely to cause allergic responses in humans.

The role of the SAP is to provide the Agency with guidance and recommendations on technical and science issues. It is not the charge of the SAP to give guidance on regulatory or policy matters. The issue before the SAP is whether or not the presence of the StarLink corn in the human food supply, in finite quantities and for a limited time duration, poses an unacceptable risk of allergenicity. Since EPA does not have sufficient expertise on the range of issues raised by the Aventis petition particularly with respect to allergenicity, EPA is raising questions for the SAP to consider in those areas where the information appears not be dispositive. Consequently, EPA's *Preliminary Evaluation* focuses solely on those science issues relevant to the StarLink petition, and does not present any final, overall conclusions about the Aventis submission. EPA and other federal agencies will consider the report from the SAP in making decisions about future regulatory actions that may be pursued by federal agencies.

The *Preliminary Evaluation* contains EPA's analysis of the information presented by the Aventis petition relating to the potential allergenicity of Cry9C. The following summarizes EPA's views on each of Aventis' principal contentions.

EPA's preliminary views regarding the potential toxicity and allergenicity of the Cry9C protein and the potential for human sensitization to the protein. There is no evidence of toxicity of either the Cry9C protein or the DNA responsible for its production. EPA also established that there is no allergenic risk to humans from eating meat, eggs, and milk from animals which might be fed StarLink corn, and therefore EPA approved a tolerance exemption for Cry9C (DNA and protein) in animal feed. EPA's only remaining concern is whether or not the Cry9C protein may pose a risk of allergenicity if directly present in the human food supply. Since EPA's initial review of this issue, Aventis has submitted several new studies and information to support its contention that the Cry9C protein is not an allergen. Based on these studies, EPA still questions whether or not Cry9C is or is not an allergen.

EPA's preliminary views regarding the potential for human sensitization to theCry9C protein. On the issue of sensitization, Aventis has presented new data that blood sera from individuals, who are sensitive to one or more of the common food allergens, do not show reactivity to the Cry9C protein. In addition, after summarizing data on the percentages of allergenic proteins in the total protein of various known food allergens (which ranged from 1% to 54%), Aventis argued that since the Cry9C protein represents less than 0.0129% of corn protein, it is extremely unlikely for there to have been sufficient exposure to cause sensitization. On the other side of this issue, members of the public have cited a new study (Bernstein, et al.) showing sensitization of occupationally exposed agricultural workers exposed to microbial sprays containing proteins belonging to the same class as Cry9C to support their view that exposure to the Cry9C protein is likely to have induced human sensitization.

After reviewing these studies, EPA still has questions on the subject of potential sensitization. EPA also questions the comparisons of Cry9C protein to known food allergens because there is no scientific basis to conclude whether Cry9C behaves in the same manner as these allergens. Finally EPA questions, the Bernstein study because the materials to which workers displayed some sensitivity differ in fundamental respects from the Cry9C protein. EPA notes that the Federal Government is actively collecting information on and investigating reports of possible adverse reactions potentially related to Cry9C in corn products.

EPA's preliminary views regarding the levels of potential dietary exposure to the Cry9C protein in processed food. The analysis of potential levels of dietary exposure to the Cry9C protein, developed and presented by Aventis in its October 25, 2000, submission, constitutes new information for EPA's assessment of the potential allergenic risk of the Cry9C protein. Although EPA does not agree completely with Aventis' approach to estimating potential dietary exposure, EPA thinks that the available information supports an overall conclusion that the potential dietary exposure to the Cry9C protein is extremely low – in the range of parts per billion or parts per trillion of food consumption by the most highly exposed individuals in the population. The

Agency seeks the SAP's views on whether Aventis has demonstrated scientifically a level of exposure below which Cry9C would not elicit an allergic response in sensitized individuals, if Cry9C behaves as an allergen.

I. The Issue:

Aventis CropScience, USA LP has amended and submitted a petition to EPA requesting a time-limited (four year), food tolerance exemption for Cry9C protein and the genetic material necessary for its production from use of StarLink corn produced in 1998, 1999, and 2000. The original Aventis petition requested unlimited use of Cry9C and the genetic material necessary for its production in all food commodities. Concerns have been raised on whether the Cry9C protein is or is not a human allergen, whether there is adequate amount of the protein in corn to cause sensitization, and what amount of Cry9C might be in the human food supply if this time limited tolerance exemption was to be approved.

Plants that are modified through biotechnology to produce and express a protein that serves as a pesticide are subject to review and registration by the EPA. As such, these plant-pesticides are regulated under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), Food Quality Protection Act (FQPA), and the Federal Food, Drug, and Cosmetic Act (FFDCA). In May, 1998, EPA approved a registration for StarLink corn, a plant-pesticide selected to control a specific group of corn insect pests, especially European corn borer. The license or registration granted to Aventis CropScience, USA LP limited the sale and distribution of the StarLink grain to animal feed and industrial uses only. Export outside of the United States was also prohibited. StarLink was the first and only registration for a biotechnology product that allowed animal feed use, but not human food use. The specific limitations of the registration, i.e. animal feed and industrial use only, were imposed because, at the time of registration, EPA lacked sufficient data to conclude that the Cry9C protein produced in StarLink corn would not be an allergen if introduced directly into the corn food chain for human consumption.

While EPA had no specific data to indicate that Cry9C was an allergen, the protein expressed in StarLink corn did exhibit certain characteristics (i.e. relative heat stability and extended time to digestion) that were common to known food allergens such as those found in peanuts, eggs, etc. EPA's concern was that StarLink corn may be a human food allergen and in the absence of more definitive data, EPA has not made a decision whether or not to register the human food use. In assessing the broader range of human and environmental impacts of StarLink corn, EPA was able to conclude that there would be no unreasonable adverse effects on the environment from its production and use and that as an animal feed, it would be safe both for cattle and poultry and for people eating food from the livestock, such as meat, eggs and milk.

In February 2000, EPA solicited outside, independent, scientific peer review by the FIFRA SAP of the data and information regarding the potential allergenicity of StarLink corn. In their June 2000 report to EPA, the SAP stated: "The panel agreed that based on the available data, there is no evidence to indicate that Cry9C is or is not a potential food allergen." The

findings and recommendations of the Panel provided insufficient scientific information to move the EPA decision on granting a human food use registration forward. The terms and conditions of the Aventis registration remained unchanged and the limitation to animal feed and industrial use remained in place. The report from a June 2000 SAP meeting on data requirements for mammalian toxicity of protein plant-pesticides also provided guidance to the Agency on allergenicity. The report was issued in October 2000. The SAP reports from all these meetings can be found at www.epa.gov/scipoly/sap.

In September, 2000, *Genetic ID,* an independent food testing laboratory, tested Kraft Taco Bell taco shells and determined that the DNA for the StarLink corn protein (Cry9C) was present in the taco shells. Subsequent testing by Kraft, FDA, and Aventis confirmed that the DNA was present in the processed food (taco shells). The presence of the StarLink protein has also been confirmed in whole corn grain. Since that time, the DNA for Cry9C protein has been detected in other brands of taco shells as well as corn flour and has been detected in multiple sources of grain across the U.S. and internationally.

While EPA believes there is no public health crisis, it is clear that the StarLink corn has made its way outside of the approved animal feed and industrial use channels and into the human food supply. The issue before the SAP is whether or not the presence of the StarLink corn in the human food supply, in finite quantities and for a limited time duration, poses an unacceptable risk of allergenicity. Advice on this issue will help guide the regulatory decisions of the federal agencies involved.

This document summarizes data and information previously submitted to the Agency and taken to the SAP for peer review regarding Cry9C and provides an assessment of data and information that has been made available since the February 29, 2000 SAP meeting on Food Allergenicity of Cry9C Endotoxin and Other Non-digestible Proteins. Following a brief review of the regulatory status of StarLink, the next three sections are: (1) the toxicity and allergenicity of Cry9C, (2) sensitization to and cross-reactivity of the protein, and (3) exposure to the Cry9C protein.

II. Current Status of StarLink:

On October 12, 2000, Aventis CropScience USA , LP (Aventis) requested the voluntary cancellation of its StarLink Corn registration. EPA accepted the Aventis request and has initiated the process to cancel the registration, but has made the decision to leave the exemption from tolerance for the animal feed use in place. StarLink corn moving through the appropriate channels of trade remains covered by that exemption from tolerance. StarLink is the only Bt corn product containing the Cry9C protein and as such is the only Bt corn product impacted by this decision.

On October 25, 2000, Aventis submitted an amendment to its original petition (PP 9F5050), for a tolerance exemption for the protein Cry9C and the genetic material necessary for

its production in food. The amended petition requested the granting of a tolerance exemption for human food use, for a limited time (four years), and based on the exposure potential associated with a finite amount of StarLink corn which might have gone into the food supply. Aventis submitted new data and analyses to support their request for this time limited exemption from tolerance. Their arguments in support of their request focus on (1) the potential for Cry9C to be an allergen, (2) the likelihood that Cry9C has been in the human food supply in large enough quantities over a long enough period of time for it to have sensitized any of the population, and (3) whether there is enough Cry9C in the food supply to trigger an allergic reaction even if the answers to (1) and (2) were to be positive. EPA has reviewed the new submission by Aventis and is making that submission, as well as additional data and information, available for public review and comment. EPA has divided its evaluation of the Aventis submission into three specific topic areas that parallel the presentation of Aventis' rationale for the exemption from tolerance: (1) the toxicity and potential allergenicity of Cry9C, (2) sensitization to the Cry9C protein, and (3) simulated exposure to the Cry9C protein through food consumption.

III. Toxicity and Allergenicity of StarLink (Cry9C):

A. Background

For all of the Bt plant-pesticides, EPA has required extensive product characterization and mammalian toxicity testing. In addition, because these substances are proteins and proteins can be human allergens, EPA has required studies and information which will screen for potential allergenicity. Among the toxicity testing required for the Bt plant-pesticides are *in vitro* studies to assess digestability and heat stability. EPA's review of the results of these two tests for the Cry9C protein identified the concern for potential allergenicity.

B. Aventis' Data Submitted and Reviewed Prior to the February 29, 2000 SAP

The following data submitted by Aventis were reviewed by EPA as part of the Aventis submission for an exemption from tolerance for human food use. These data were also included in the background material provided to the February, 2000 SAP that met specifically to address Cry9C and the issue of allergenicity. The data identified in the first table describe the protein, expression levels, and other relevant protein characterization information. The second table provides summaries of Aventis' studies of toxicity and allergenicity testing performed on Cry9C. All the information is cited by EPA's Master Record Identification Number (MRID #). The studies which do not contain confidential business information on the manufacturing process are available in the EPA Docket.

Table 1: Product Characterization of Cry9C

Study Type	***MRID #***
Grain Composition	442581-04

Study Type	*MRID* #
Protein Characterization and Expression	442581-05
Insect Host Range Comparison of Cry9C Protein.	442581-06
Protein Characterization and Expression	443844-01
Protein Characterization and Expression	443844-02
Transformation System Characterization of the DNA Inserted in the Plant	442581-01
Characterization of the DNA Inserted in the Plant	443844-03

Table 2: Toxicological Endpoints of Cry9C Corn

Study	MRID #
An Acute Oral Toxicity in Mice with Cry9C Protein as Purified from *Bacillus thuringiensis* Cry9C.PGS2	442581-07
In vitro Digestibility and Heat Stability of the Endotoxin Cry9C of *Bacillus thuringiensis*	442581-08
Cry9C *Bacillus thuringiensis* Insecticidal Protein Identification of Sequence Homology with Allergenicity by Searching Protein Databanks	443844-04
Investigation of Allergens in Wild-Type and Transgenic Corn	443844-05
Amino Acid Sequence Homology Search with the Corn Expressed Truncated Cry9C Protein Sequence	442581-09
Safety Assessment for StarLink Corn Containing Cry9C for Human Food Use	447140-01
Cry9C Protein Potential for Binding to Mouse Intestinal Brush Border Cells	447343-01
Cry9C Mouse Acute Intravenous Toxicity	447343-02
Mouse Short-term (30-day) Dietary Toxicity with Cry9C	447343-03
Stability of PAT and Cry9C Protein in Processed Grain of Transgenic Corn in Fractionated Agricultural Commodities	447343-04

Development of New Methodology for Safety Evaluation of Transgenic Food Crops	447140-02
Occupational Exposure of StarLink Corn: Garst Seed Company 1996-1998	447140-03
Assessment of Stability to Digestion and Bioavailability of Cry9C Protein	447343-05

The mammalian toxicity data for Cry9C demonstrated that the protein was not toxic to mammals even at high dose levels. Proteins that demonstrate toxicity are known to act via acute mechanisms and at low doses. Because of the lack of Cry9C toxicity, EPA did not require mutagenicity, developmental toxicity, subchronic toxicity, chronic exposure and oncogenicity studies to be submitted. This approach was taken to an SAP meeting in June 2000. In their report, SAP members indicated in part that, "the maximum hazard dose approach is generally adequate to address protein toxicity." A copy of the SAP report of that meeting has been included for SAP panel members and is available on the SAP web site (www.epa.gov/scipoly/sap).

EPA concluded that the DNA necessary for the production of Cry9C lacks the potential to cause allergic reactions. It is commonly agreed upon in the scientific community that DNA has no history of toxicity, that nucleic acids are ubiquitous in the food supply, and DNA is common in all forms of plant and animal life. EPA concluded that based upon the overall safety of DNA, there were no anticipated toxicity or allergenicity concerns from ingestion of the *cry9c* gene or DNA itself.

Regarding allergenicity of the protein, EPA has concluded that Cry9C is not likely to cause an allergic reaction in humans when StarLink corn is used as animal feed. However, because Aventis also sought an exemption from the requirement of a tolerance for food use, EPA brought a number of scientific questions to an SAP panel on February 29, 2000. The questions were based on potential allergenic characteristics identified during review of the data listed above. Specifically, the *in vitro* digestibility study indicated that the protein was stable in simulated gastric fluid for up to 4 hours at pH 2. Also, the protein was relatively resistant to heat (90° C for 10 minutes). The Agency is aware that no protein was detected by the company in catfish food after the corn was processed into food pellets (MRID# 443843-01). *In vitro* digestibility and heat stability have been identified as two common characteristics of protein food allergens. Because of this, additional consideration is required to determine the potential allergenicity of the protein, especially one without a history in the human diet.

An additional study submitted by Aventis the RAST study which compared blood serum from corn sensitive individuals with Cry9C antigens, did not support an allergenicity finding. However, this study may not be of value without documented human dietary exposure to the Cry9C protein. Based upon the data listed above and known scientific knowledge about protein

food allergens, SAP panel members concluded in part in their report from the February 29, 2000 meeting (released June 29, 2000) that "there is no evidence to indicate that Cry9C is or is not a potential food allergen."

C. Materials Submitted Since the February SAP Meeting

Additional data has been submitted by Aventis since the February SAP meeting and has been subsequently reviewed by the Agency. The following table identifies each of these studies.

Table 3: Cry9C Studies Submitted Since February SAP Meeting

Study	MRID#
Phosphinothricin Acetltransferase and Cry9C Protein Content in Processed Fractions of Transgenic Field Corn Event CBH351, USA, 1998	450257-01
In vitro Digestibility of Cry9C protein by Simulated Gastric and Intestinal Fluids	451144-01
In vitro Digestibility of Endotoxin Cry9C derived from *E. coli* and *B. thuringiensis*	451144-02
Analysis of Taco Shells for CBH351 (Cry9C) DNA	452402-01
Analysis of Taco Shells for CBH351 (Cry9C) DNA	452402-02
Preliminary Study for Detection of Cry9C Protein in Taco Shells	452402-03
Preliminary Report Evaluation of IgE Antibody Reactivity of Food-Allergenic Subjects to StarLink Corn	452464-01
Analysis of Taco Shells for Cry9C Protein	452464-02
Updated Safety Assessment of StarLink Corn Containing Cry9C Protein	452465-01

Aventis recently submitted additional *in vitro* digestibility studies which indicate that Cry9C protein stability is significantly affected by pH conditions of the simulated gastric fluid. As shown previously and in newly submitted data, at pH 2.0, the protein is stable for more than four hours. However, simulated gastric fluids prepared at lower pH appear to reduce protein stability. Although the newly submitted data (gel figures) do not allow for a definitive conclusion, it appears that at pH 1.2 and 1.5, the protein is stable for at least 30 minutes with no protein apparent after that time point. As part of their petition for a food tolerance for Cry9C, Aventis suggests that this reduced stability decreases the exposure time in the intestines to a

point where concern about allergenicity is eliminated.

However, consideration must also be made of the relationship between stomach pH and the time necessary to pass through the stomach because these factors are essential to determine the likely gastrointestinal exposure and degradation of the Cry9C protein. Gastric pH in normal fasting individuals can vary from less than 1.0 up to 3.0, a one hundred fold difference in acidity. This pH can be raised significantly, but temporarily, by ingestion of food, antacids, or medications. EPA does not have data on the distribution of individuals with different gastric pH levels. Likewise the transit time for the stomach also varies in normal populations depending on the period of fasting to the amount of food ingested. The average transit time through the stomach is approximately one hour with passage being as short as 15 minutes for a small item on an empty stomach up to four hours for a full meal (J. Fallingborg, 1999; T.L. Russel *et al.*, 1993; D.F.Evans *et al.*, 1988; J. Fallingborg *et al.,* 1990). Thus, even if Cry9C protein is stable for only 30 minutes at pH 1.2, it allows for exposure for that period of time in individuals with low gastric pH, and even longer times for those with higher gastric pH. Because of this, EPA questions whether the additional *in vitro* digestibility data resolves the issue of potential allergenicity based upon variability in gastric pH and transit time of individuals.

IV. Protein Sensitization and Cross-Reactivity:

A. Background

In order for a person to have an allergic reaction to a protein, the person must first become sensitized to that protein. Sensitization involves being exposed to a protein at high enough concentrations and over an extended period of time to develop an allergic reaction. This sensitization can happen *in utero* or later on in life, especially if the protein is newly introduced into the diet.

The Cry9C protein is not found in any microbial pesticide products approved for use in the United States. The *Bacillus thuringiensis* subspecies *tolworthi* bacterium which produces Cry9C was isolated in the Philippines and it is unknown if the subspecies could be found in the United States. The October 25, 2000 Aventis submission states that two registered microbial products contain a related Cry9B protein. EPA has contacted the two registrants of these products and both the companies state that their products do not produce any Cry9 proteins. Available information indicates that Cry9B and Cry9C are only 60 to 70 % homologous. Based upon data available to the Agency, it is unlikely that there have been exposures to the U.S. population from sources other than StarLink corn. Moreover, a time-limited tolerance reflects the fact that no additional Cry9C will go into the food supply.

Experts have advised EPA that typically, but not necessarily always, dietary proteins which are food allergens represent more than 1 percent of the total protein in the food. In the case of Cry9C in corn, approximately 0.0129% of the total corn protein is Cry9C. The Aventis petition contends that extremely low levels of a protein in a food may represent a minimal

potential for sensitization to that protein.

B. Aventis' Data Submitted and Reviewed Prior to the February 29, 2000 SAP

Only one study submitted by Aventis and reviewed by EPA previous to the February SAP meeting provides any information dealing with sensitization. This was a radioallergosorbent (RAST) test identified in Table 3. This test indicated blood sera from that individuals allergic to corn were no more likely to react to StarLink corn than to non-StarLink corn. This study does not provide a definitive answer to sensitization, but contributes to the weight of evidence that the US population has not already been sensitized to Cry9C by levels that may occur in the environment.

C. Recently Submitted Materials

1. Aventis Studies

One additional study was submitted by Aventis which considered sensitization of individuals with known reactions to common food allergens (such as those found in buckwheat, eggs, milk, peanut, rice, shrimp, soy, and wheat) and the potential for cross reactivity to the Cry9C protein. Basically, blood serum from patients with common food allergies did not react with Cry9C. Aventis believes this study indicates that it is unlikely that people with common food allergies are likely to already be sensitized to Cry9C. It does not address long term sensitization to the protein.

Aventis has also submitted a dietary analysis of peanut protein correlating the normal population's dietary exposure to the allergenic proteins in this potent food allergen to the potential dietary exposure scenarios for the Cry9C protein. The basis for the peanut dietary analysis is a paper (J. Hourihane *et al.*, 1997) where the threshold level of 14 clinically verified peanut sensitized individuals was examined in a food challenge. The paper reports that as little as 16 micrograms of the Ara h1 and Ara h2 protein in 100 micrograms of peanut protein can elicit a subjective reaction in some of these peanut sensitive subjects. A dose of 2 milligrams (320 micrograms of the offending allergens of the Ara h1 and Ara h2 protein) can cause a clinically observable reaction in some of the subjects. The inferences of a study of 14 individuals to the responsiveness of the entire population of peanut sensitive people are questionable but are certainly the best estimates available.

Using these experimentally derived values of 16 micrograms of peanut protein for a mild and subjective reaction, the company claims all their dietary exposure scenarios for the current StarLink misdirection incidents result in far lower exposures to the Cry9C protein. The company's "worst case" upper values for StarLink dietary exposure are stated as being 6.4 to 8.6 micrograms of Cry9C protein. While the Agency does not believe there is any indication that Cry9C protein could be as potent a food allergen as the peanut allergens, it is not certain of the utility of making such a dietary comparison between peanut allergen and Cry9C protein. EPA is

also uncertain of comparing the dietary patterns of the normal population for the peanut protein to address the sensitizing level of a potential allergen. Finally, EPA's dietary analysis show several scenarios that it believes approach or exceed the stated subjective reaction threshold of 16 micrograms for the Cry9C protein (see Section V., Tables 9 to 13). None of EPA's dietary analysis scenarios approaches the clinical reaction threshold of 320 micrograms of the peanut allergens.

The Agency seeks the SAP's views on whether this data and the time limited nature of the petition provide a basis to determine whether the US population has been or will be exposed in a manner likely to cause sensitization.

2. Public Studies and Information

A recent article by I.L. Bernstein *et al.* has been cited by a number of public commenters as being a useful method to assess the allergenicity of the Cry9C proteins expressed in food crops. While the cited study is very useful for addressing the possible sensitization of individuals in occupational settings to *Bacillus thuringiensis* microbial pesticide preparations, the Agency feels it is inappropriate to address the food allergenicity of the Cry9C protein expressed in StarLink corn due to several confounding factors. The thrust of the Bernstein article is to address dermal and inhalation sensitization in people exposed to the entire *Bacillus thuringiensis* bacterium. While oral exposure is certainly a part of the inhalation exposure, the study does not provide the means to examine the food allergy to a specific protein of the microbial preparation separately. The study focused almost solely on looking at preparations derived directly from the microbial pesticides. As a consequence, numerous bacterial proteins were in fact present in the test compound. Even the described protein extract, which gave the least number of skin positive responses, would be expected to contain significant amounts of other bacterial proteins. Moreover, the Cry9C protein is not presently found in any of the *Bacillus thuringiensis* microbial pesticides currently registered.

EPA issued a Federal Register Notice on October 31, 2000 announcing receipt of new information from Aventis on October 25, 2000 and requesting public comment on the information. In addition, the Federal Register Notice asked for anyone having information concerning any allegations of adverse effects in humans from ingestion of foods that might contain StarLink corn to submit that information to the Food and Drug Administration (FDA). EPA, the United States Department of Agriculture (USDA), and the FDA sent a letter to the food industry requesting that they provide the Federal agencies with any information the food industry has on adverse reactions to food products which might reasonably be related to StarLink. In addition, the Centers for Disease Control and Prevention (CDC) and the FDA are compiling incident reports of any one reporting an adverse reaction that might have been exposed to Cry9C. CDC and FDA are investigating these incidents and will be reporting on their results at the November SAP meeting.

V. Estimating Potential Human Exposure to Cry9C Protein in Processed Food:

Aventis' submission contains extensive information concerning the potential dietary exposure to Cry9C in processed food made from StarLink grain. This portion of the submission represents new information and is related to Aventis' contention, discussed elsewhere, that the levels of Cry9C protein expected in the diet are not sufficient to cause allergic reactions, much less to cause sensitization. The following discussion begins with a discussion of Aventis' basic approach to estimating potential dietary exposure to Cry9C protein. The second section discusses the critical assumptions regarding the extent to which StarLink grain is co-mingled with non-StarLink grain. The last section contains several alternative estimates by EPA of the potential exposure to the Cry9C protein.

A. Overview of Methods for Estimating Potential Dietary Exposure

EPA agrees with Aventis that the level of potential dietary exposure to the Cry9C protein is a function of the amount of food containing Cry9C consumed and the level of the protein in processed food. The level of the Cry9C protein in processed food depends on: (1) the initial residue level of the Cry9C protein in corn, (2) the extent to which StarLink and non-StarLink grain were mixed, and (3) the effects (if any) of processing on the level of Cry9C protein as com grain is made into processed food. Each of these elements is discussed below.

1. Consumption of Food That May Contain Cry9C Protein

EPA believes that the data from the USDA's Continuing Survey of Food Intake by Individuals (CSFII) ('94 – '96, 98) provides the best information to estimate the daily individual intake of processed foods. Like Aventis, the EPA assessment of dietary exposure takes into account only consumption of food made using the ingredients, corn bran and corn endosperm, that retain protein after processing. (Corn syrup, corn oil, and other food forms made from corn grain contain virtually no protein.) EPA also agrees with Aventis' caution about the statistical reliability of some of the higher percentiles of daily consumption that are based on limited numbers of responses and the limited number of responses for infants.

Table 4: Per Capita Estimates of Daily Whole Corn Grain Consumption in g/day.

Population Subgroup	95th Percentile	99th Percentile	99.9 Percentile
US Population	62	129	293
Hispanic Population	88	172	317
Hispanic children 1-6 years	47	79	153
Hispanic children 7-12 years	90	122	287
All infants (<1 year)	12	47	55
All children, 1-6 years	40	68	146

All children, 7-12 years	62	109	331

2. Level of Cry9C Protein in Grain from Starlink Corn and the Associated "Buffer Corn"

Aventis's submission used the value of 0.0129% for the concentration of Cry9C protein in corn expressed as a percentage of the total protein found in corn. EPA, however, uses 12.9 ppm of Cry9C protein expressed in StarLink corn grain. Aventis's value of 0.0129% Cry9C protein of total corn protein is a calculated correction of the experimentally obtained value to provide a different expression for the amount of total protein in corn grain which is Cry9C. EPA's value is based directly on the reported micrograms of Cry9C protein found in weighted samples of whole corn grain. EPA also typically refers to ppm values when discussing pesticide residues and believes the public is familiar with that method of expressing exposure.

Also, because pollen from StarLink corn may drift onto nearby corn and cause expression of the Cry9C protein in these plants, the EPA approval of the StarLink registration required that grain from all corn planted within 660 feet of StarLink plants be handled in the same manner as StarLink grain. While grain from these "buffer" plants may contain some Cry9C protein, the Agency does not have sufficient direct measurements of Cry9C protein levels to develop a precise estimate. The Agency is able to use other information -- data on the distances that corn pollen will drift, as well as data regarding hybridization isolation distances -- to conclude that the average level of Cry9C protein in "buffer corn" is likely to be lower than in StarLink corn. Based on its evaluation of pollen drift, EPA conservatively estimates that approximately one-third of grain from buffer plants will contain Cry9C protein, and without better information the Agency assumes that the level of Cry9C protein in such buffer plants is 12.9 ppm. (Aventis' submission contains a couple of scenarios that considered the potential contribution to exposure of Cry9C protein in "buffer corn," but the method by which the scenarios were calculated makes any comparison with EPA's assessment uncertain.) Therefore EPA has adjusted the yield of the "buffer corn" acreage to reflect that only one third of that grain is expected to contain Cry9C protein.

3. Effects of Mixing Starlink and Non-Starlink Corn Grain

EPA is unable at this time to confirm exactly how much mixing of StarLink and non-StarLink corn may have occurred. It is clear, however, that the amount of the Cry9C protein potentially present in processed foods will be "diluted" by the "co-mingling" or mixing of StarLink and non-StarLink corn grain. As discussed below in section B., the information presently available does support some preliminary characterization of the impact of mixing. In the meantime, EPA's upper bound estimates are about 7 times higher than Aventis' highest estimates. Aventis' highest estimates are similar in magnitude to EPA's lower estimates.

4. Effects of Processing on Levels of Cry9C Protein

Estimating the amount of Cry9C protein in the processed food is difficult since EPA has limited information about the extent to which the Cry9C protein remains in processed foods made from StarLink corn. Aventis submitted new data containing a small number of direct measurements of the levels of the Cry9C protein in processed food, but these used an analytical method that has not been validated. The analyses detected no Cry9C protein with a limit of sensitivity of 4.7 ppb. As discussed earlier, the Cry9C protein is somewhat stable under high temperature. While EPA thinks the protein may be degraded by the high temperatures used for baking and frying, but EPA does not have data to confirm this belief. In the production of some processed foods, however, corn grain undergoes additional steps that might reduce or eliminate the Cry9C protein. Additional information available to EPA on the stability of Cry9C under heat comes from an Aventis study of the effect of "pelletizing" corn grain to produce catfish feed which indicates that this type of high heat processing either destroys all Cry9C protein or reduces the levels below the limit of detection. The limit of detection was not reported in the fish feed study and the study contained very little information on the analytical method used.

In the absence of better information, EPA will use the conservative assumption that the Cry9C protein is completely retained in finished processed food products. EPA regards this assumption as likely to overstate potential exposure because it is possible that some types of processing may degrade Cry9C protein and thus reduce or even eliminate the substance. In sum, EPA believes it is prudent to assume that the amount of the Cry9C protein in corn, 12.9 ppm, will remain in the processed food at the same concentration in the corn ingredients coming from StarLink corn.

5. Summary

Aventis and EPA have taken similar approaches to estimating dietary exposure to Cry9C protein in processed food. The Agency differs from Aventis with regard to: (1) the level of Cry9C protein in corn, (2) the assumptions about how to handle "buffer corn," and (3) the assessment of the impacts of mixing. First, EPA and Aventis differ by a factor of 10 on the level of Cry9C protein in corn grain. Second, EPA's assumptions relating to "buffer corn" result in an estimate of 16% more grain that may have Cry9C than most of Aventis' scenarios, but the difference between the two approaches does not appear to be significant. Finally, the impact of assumptions about mixing may be more significant as discussed below in section B. EPA acknowledges that it has used conservative assumptions which have resulted in EPA's and Aventis' estimates differ by about 7 fold.

B. Evaluating the Effects of Mixing StarLink and Non-StarLink Corn Grain

1. Aventis' Approach to Mixing

EPA believes that the most important variable affecting an individual's exposure is the

amount of Cry9C in the individual's diet, and this value depends significantly on the extent of mixing of StarLink and non-StarLink grain. Aventis characterizes its exposure estimates as "worst case" because Aventis contends its assumptions about the amount of StarLink corn in the human food supply and how this grain is mixed with non-StarLink grain are conservative.

Aventis' submission contained an appendix that described many steps from the harvesting of grain to the production of milled grain fractions during which StarLink corn could be co-mingled with non-StarLink corn. Using examples and expert judgment, the submission argued that, because co-mingling occurs at so many stages of the process of converting grain into processed food, it is reasonable to assume that StarLink and non-StarLink corn grain are evenly mixed in the human food supply. Thus, Aventis assumes that the ratio of StarLink to non-StarLink corn in any processed food item is proportional to the ratio of StarLink grain to non-StarLink grain in the overall human food supply.

Aventis presents several scenarios to account for different possibilities concerning the amount of StarLink corn that has entered the human food supply. In general Aventis starts with the acreage of StarLink corn grown each year, expressed as a percentage of the overall US field corn crop. These "percentage StarLink" values are presented in Table 5, below.

Table 5. StarLink Production Compared to US Corn Production

Year	Total US Field Corn Crop (Acres)	Total StarLink Crop (Acres)	StarLink as a Percentage of National Field Corn Crop Acreage
1998	80.2 million	9,018	0.01%
1999	77.4 million	247,694	0.32%
2000	79.6 million	350,420	0.43%

To produce its estimates of exposure for a particular year, Aventis multiplied the "percentage StarLink" by the amount of StarLink corn that could possibly have entered the human food supply during that year. Aventis calculated exposure based on the following range of assumptions: for the 2000 crop, 12% (the portion of the 2000 crop that could not be accounted for before the date of the submission) or 50% (a higher value intended to take into account the presence of Cry9C protein in "buffer corn") and for the 1999 crop, 13% (the portion of the nation corn production that is directed to any type of human food, including foods that do not contain protein) or 50% (a higher value intended to take into account the presence of Cry9C protein in "buffer corn"). The Aventis estimates of the impacts of mixing and compliance appear in Table 6, below:

Table 6: Aventis Estimate of Percentages of StarLink in Corn Grain in the Human Food Supply

Year	StarLink Acreage as a Percentage of National Field Corn Crop	Percentage StarLink Possibly Entering Human Food Supply	Percentage of StarLink in Corn Grain in the Human Food Supply
1999 (13% assumption)	0.32%	13%	0.04%
1999 (50% assumption	0.32%	50%	0.16%
2000 (12% assumption)	0.43%	12%	0.04%
2000 (50% assumption)	0.43%	50%	0.22%

These values also could be expressed as representing a co-mingling of each bushel of StarLink grain with about 2500, 625, or 450 bushels of non-StarLink grain for: '99 (13%) and '00 (12%); '99 (50%); and '00 (50%), respectively.

Using the above information, data on consumption of foods containing corn protein, and a value of 1.29 ppm for the residue level of Cry9C protein in processed food, Aventis obtained the following estimates of exposure.

Table 7: Aventis Estimates of Daily Exposure to Cry9c Protein for 1999 Assuming 13% of the StarLink Crop Entered the Human Food Supply (adapted from Aventis' submission's Table 5).

Group	Daily Exposure in Micrograms of Cry9c Protein		
	Exposure for 1999		
Percentile:	95th	99	99.9
Hispanic	0.4	0.9	X
Hispanic Children 7-12	0.5	X	X
Hispanic Children 1-6	0.2	X	X
US Population	0.3	0.6	1.5
Children 7 to 12 yrs	0.3	0.5	X
Children 1 to 6 yrs	0.2	0.3	X

X = data are not sufficient to permit statistically reliable estimates of exposure at this percentile

The exposure estimates for other years and scenarios would increase arithmetically in proportion to the percentage of StarLink grain assumed to be present in the human food supply. Thus, the estimated exposures for 2000 (assuming 50%) would be about 5.5 times higher for each percentile and population group.

In EPA's view, the Aventis' approach does not necessarily represents a "worst-case" approach. Aventis' data suggest that the extent of mixing may be considerably more limited than its exposure estimates assume. A few days after its October 25 submission, Aventis submitted a survey of the commingling rates from 33 off-farm elevators in 7 states. The results of this survey indicate that StarLink corn was present in grain elevators at concentrations ranging from 0.25% to 62.5%. The average Starlink concentration in these elevators was 3.5%. Four elevators (out of 33) had concentrations of 48% or higher. The next 5 highest had concentrations ranging from 9 to 17%. One explanation that Aventis offered for these high concentrations was that these elevators deliberately segregated StarLink corn for shipment to feed lots or industrial plants (and thus complying with the label). However, even if the four highest values are removed from the distribution, the average grain concentration in these elevators is 2.8% (a ratio of 1 bushel of StarLink grain to about 35 bushels non-StarLink grain) -- a concentration that is considerably higher than the 0.04% or 0.22% assumptions used in Aventis' exposure estimates. These higher percentages are consistent with the advice of experts discussed below.

In addition, EPA does not think that the level of Cry9C protein in co-mingled grain would be affected by whether some portion of that grain is directed to feed uses. Therefore, EPA does not agree with Aventis' methodology of estimating levels of Cry9C protein by multiplying the ratio of mixed StarLink and non-StarLink grain by the fraction that is assumed to have entered the human food supply. No matter what portion of the co-mingled grain enters the human food supply, once the overall ratio of StarLink grain to non-StarLink grain is established (whether in the storage facility or at a mill) EPA expects that ratio to remain nearly constant at further steps in the process of making finished food products. As discussed below, the Agency has used a different approach to account for the degree to which StarLink corn was directed to animal feed or industrial uses.

2. EPA's Preliminary Approach to Mixing

Agency scientists have been working with experts knowledgeable in the field of corn harvesting, storage, milling, and processing to gain a better understanding of the potential for mixing of StarLink and non-StarLink grain and grain products. These discussions have led the Agency to a better qualitative understanding of the potential for co-mingling at different steps of the process. Briefly, the information indicates that the scale of production of StarLink from individual farms and the scale of operation of different storage, milling, and processing facilities assures some level of mixing, but make it unlikely that there will be uniform mixing on a national scale. The experts advise that corn growers usually send their crops to local milling and

processing facilities, and therefore the composition of corn grain products from a particular milling or processing facilitiy will reflect the concentration of StarLink corn in the facility's local supply area. In summary, the experts' information indicates that the degree of mixing may differ from lot to lot, depending on factors such as the relative local percentage of StarLink and non-StarLink corn, the size of storage facilities, the size of milling facilities, and the number of times that lots of grain are combined during the storage or milling process.

While this available information is not sufficient to support a precise quantitative estimate of the distribution of mixing scenarios, EPA has reached a preliminary conclusion regarding the high end of the distribution of mixing. EPA recognizes that the percentage of the corn crop that is StarLink likely varies from place to place, and has chosen to use the highest state values for 1999 and 2000 as its estimates of the high end of the distribution of levels of Cry9C protein in corn grain and corn grain products. Specifically, EPA selected 1.2% (i.e. about a 82:1 mix of non-StarLink and StarLink grain) and 1.5% (i.e. about a 66:1 mix of non-StarLink and StarLink grain) in 1999 and 2000, respectively. (Brassard, 2000; estimates of mixing at the 90^{th} to 98^{th} percentile.) These values are about three to four times higher than the overall percentage acreage planted with StarLink corn in the national crop for 1999 and 2000. Compare Table 5. Use of these values assumes that whatever amount of StarLink grain was used to make processed food was present in the same percentage as it was planted in a particular state. Because this assumption does not take into account the impact of grower compliance with the animal feed restriction in 1999 and 2000 or the actions taken by Aventis and USDA to divert 94% of the 2000 crop to approved uses, the assumption likely overstates potential exposure.

Recognizing that compliance may affect exposure, EPA also has attempted to assess the impact of actions that directed StarLink grain to animal feed uses. For the 2000 crop, the Agency has some information to estimate the amount of StarLink corn that has directly entered the human food supply and thus, the potential for it to be mixed with non-StarLink grain. The recent actions taken by Aventis and USDA have successfully resulted in placing approximately 88% of the 2000 Star Link corn crop under USDA's direct control. In addition, Aventis has located and determined that an additional 6% of the 2000 crop was directed to animal feed use. Thus, at present, the Aventis – USDA program cannot account for six percent of the 2000 StarLink crop or 4.8 million bushels of corn. Some or all of this corn may have entered the human food supply, after mixing with non-StarLink grain. EPA believes that it is reasonable to assume that the 4.8 million bushels of StarLink grain has been mixed with the 3,400 million bushels of non-StarLink grain from the 2000 crop that had left the farm prior to October 1, 2000. Based on this information, EPA thinks that a reasonable estimate of the portion of grain from the 2000 corn crop in the human food supply that is StarLink to be 0.14%. This percentage would be the case no matter whether all of the co-mingled grain entered the food supply or only some portion of it.

Because Aventis is unable to verify what proportion of the StarLink crops in 1998 and 1999 may have been misdirected to the human food supply, EPA has less information on which to base its estimates for those years. (Given the extremely small acreage of StarLink in 1998, the

Agency did not develop an estimate for 1998.) EPA has developed an estimate for 1999 of the percentage of StarLink in human food based on different assumptions concerning the extent of compliance with the requirement that StarLink grain not be allowed to enter the human food supply. The method of performing these calculations is described in Appendix 1. The high end estimate of compliance is 99%, resulting in a percentage of the grain in the human food supply that is estimated to be StarLink of 0.006%. At the low end of compliance (assuming only 60% of StarLink grain was directed to animal feed uses), the percentage of the grain in the human food supply that is estimated to be StarLink becomes 0.23%.

Table 8. Summary of EPA's Assumptions Concerning Mixing of StarLink and non-StarLink Grain

EPA's Assumptions	Percentage of the corn grain in the human food supply that may be StarLink
1999 – Upper bound end estimate of exposure assuming complete mixing of StarLink and non-StarLink grain in proportion to the highest percentage of corn acreage planted to StarLink in any State in 1999	1.2%
1999 – Estimate of exposure assuming 60% compliance with feed use restriction and subsequent complete mixing of StarLink grain in the human food supply with non-StarLink grain	0.23%
1999 -- Estimate of exposure assuming 99% compliance with feed use restriction and subsequent complete mixing of StarLink grain in the human food supply with non-StarLink grain	0.006%
2000 – Upper bound estimate of exposure assuming complete mixing of StarLink and non-StarLink grain in proportion to the highest percentage of corn acreage planted to StarLink in any State in 2000	1.5%
2000 – Estimate of exposure assuming 94% compliance with feed use restriction and subsequent complete mixing of 4.8 million bushels of StarLink grain with 3,400 million bushels of non-StarLink grain	0.14%

C. Bounding Estimates for Human Dietary Exposure to Cry9C

Because of the uncertainty about the extent of mixing of StarLink and non-StarLink corn

grain, EPA has developed several "bounding estimates" of the levels of Cry9C in food. EPA calculated each potential dietary exposure to the Cry9C protein as follows:

Consumption of foods retaining corn protein	X	Residue level of Cry9C protein in corn	X	Estimated % StarLink for corn used in food (also called mixing factor)

All of the estimates use the same data on food consumption (see Table 4) and level of Cry9C in corn (12.9 ppm); they differ only in the values used to reflect the extent of mixing. Compare Table 6 and 8.

All tables show the same basic information: the daily exposure in micrograms of Cry9C protein for the general U. S. Population and six subgroups – Hispanics of all ages, Hispanic children 7 to 12 years, Hispanic children 1 to 6 years, Children 7 to 12 years, Children 1 to 6 years, and Infants. For all groups, the Agency estimated the consumption of Cry9C at the 95th percentile; in other words, for that particular group, 19 of 20 individuals would consume less processed food containing corn protein (and thus less Cry9C) than the amount estimated. In addition, each table contains an estimate of the 99th and 99.9th percentile of exposure for those groups for which the food consumption data support a statistically reliable estimate. Although not considered statistically reliable, EPA has included an estimate of the 95th percentile exposure of infants because of public concern about this age group.

Tables 9 and 10 assume for 2000 and 1999, respectively, an upper end concentration of StarLink grain in the human food supply. These estimates also assume that all of a person's daily ingestion of corn-based protein comes only from grain that contains this relatively high percentage of StarLink corn. This is an upper bound estimate; EPA does not expect people to receive higher exposures than these estimates. In addition to the reasons concerning the potential effects of processing on the level of Cry9C protein in food discussed earlier, exposures are likely to be lower for the vast majority of the population because: 1) 95 or 99.9 percent of the population eats less food containing corn protein than used in these estimates, 2) some portion of the corn protein may come from grain that contains a smaller percentage of StarLink grain, and 3) some of the corn protein may come only from non-StarLink corn.

The estimates in Tables 11, 12, and 13 assume that all of the StarLink corn, reasonably estimated to be present in the human food supply, is uniformly mixed with non-StarLink corn and that all corn-based protein in a person's diet reflects this mixture. EPA believes that there are places where StarLink corn would occur in higher percentages than if there was uniform mixing of StarLink corn and non-StarLink corn on a national basis, and therefore, this aspect of the calculation tends to understate somewhat the potential exposure to some people consuming food made in part from StarLink corn. These tables also reflect consideration of information about the impact of efforts to direct StarLink grain to animal feed use.

Table 9. Estimated Upper Bound Exposure for Various Population Groups for 2000 Assuming Food Containing Corn Protein Was Made from Grain Containing 1.5% Starlink Corn

Group	Daily Exposure in Micrograms of Cry9C Protein		
	Upper Bound Exposure for 2000 (1.5%)		
Percentile:	95	99	99.9
Hispanic	17	33	X
Hispanic children 7-12	17	X	X
Hispanic children 1-6	9	X	X
US Population	12	25	57
Children 7 to 12 yrs	12	17	X
Children 1 to 6 yrs	8	11	X
Infants	2 X	X	X

X= data are not sufficient to permit statistically reliable estimates of exposure at this percentile

Table 10. Estimated Upper Bound Exposure for Various Population Groups for 1999 Assuming Food Containing Corn Protein Was Made from Grain Containing 1.2% Starlink Corn

Group	Daily Exposure in Micrograms of Cry9c Protein		
	Upper Bound Exposure for 1999 (1.2%)		
Percentile:	95	99	99.9
Hispanic	14	27	X
Hispanic Children 7-12	14	X	X
Hispanic Children 1-6	7	X	X
US Population	10	20	45
Children 7 to 12 yrs	10	17	X
Children 1 to 6 yrs	7	11	X
Infants	2 X	X	X

X= data are not sufficient to permit statistically reliable estimates of exposure at this percentile

Table 11. Estimated Exposure for Various Population Groups for 2000, Assuming Food Containing Corn Protein Was Made from Grain Containing 0.14% Starlink Corn

Group	Daily Exposure in Micrograms of Cry9C Protein		
	Exposure for 2000 Assuming 0.14%		
Percentile:	95	99	99.9
Hispanic	1.6	3.1	X
Hispanic Children 7-12	1.6	X	X
Hispanic Children 1-6	0.8	X	X
US Population	1.1	2.3	5.3
Children 7 to 12 yrs	1.1	2.0	X
Children 1 to 6 yrs	0.7	1.2	X
Infants	0.2 X	X	X

X= data are not sufficient to permit statistically reliable estimates of exposure at this percentile

Table 12. Estimated Exposure for Various Population Groups for 1999, Assuming Food Containing Corn Protein Was Made from Grain Containing 0.23% Starlink Corn

Group	Daily Exposure in Micrograms of Cry9C Protein		
	Exposure 1999 with 60% Compliance (0.23%)		
Percentile:	95	99	99.9
Hispanic	2.6	5.1	X
Hispanic Children 7-12	2.7	X	X
Hispanic Children 1-6	1.4	X	X
US Population	1.8	3.8	8.7
Children 7 to 12 yrs	1.8	3.2	X
Children 1 to 6 yrs	1.2	2.0	X
Infants	0.4 X	X	X

X= data are not sufficient to permit statistically reliable estimates of exposure at this percentile

Table 13. Estimated Exposure for Various Population Groups for 1999, Assuming Food Containing Corn Protein Was Made from Grain Containing 0.006% Starlink Corn

Group	Daily Exposure in Micrograms of Cry9C Protein		
	Exposure 1999 with 99% Compliance (.006%)		
Percentile:	95th	99	99.9
Hispanic	0.07	0.10	X
Hispanic Children 7-12	0.07	X	X
Hispanic Children 1-6	0.04	X	X
US Population	0.05	0.10	0.23
Children 7 to 12 yrs	0.05	0.08	X
Children 1 to 6 yrs	0.03	0.05	X
Infants	0.01 X	X	X

X= data are not sufficient to permit statistically reliable estimates of exposure at this percentile

APPENDIX 1

To estimate the potential mixing of StarLink with non-StarLink grain in 1999, EPA needed to estimate the amount of StarLink grain produced, the portion of that grain that may have entered the human food supply, and the amount of non-StarLink grain with which it may have been combined.

1. The amount of StarLink grain produced in 1999 is indicated in the table below; for convenience, information on the production in 1998 and 2000 is also included. Please note that the bushels of production reflects EPA's assumption that only 1/3 of the "buffer corn" will contain Cry9C.

	Total US Corn Production		Cry9C Corn Production				Percent of U.S. Crop in Bushels		
Year	Acres	Bus.	Acres	Buffer	Total Acres	Total Bushels**	Cry9C	Buffer	Total
1998	80.2 M	9.8 B	9,018	4,149*	13,167	1,606,128	0.01	<0.01	0.02
1999	77.4 M	9.4 B	247,694	116,417*	364,111	44,114,931	0.41	0.06	0.47
2000	79.6 M	10.1 B	350.420	164,101	514,521	62,410,692	0.53	0.08	0.62

* buffer areas were estimated using 47% of the StarLink planted acres

** buffer crops are based on a 33% yield of Cry9C containing kernels from the pollen spread scenario discussed in section V. A. 2.

2. EPA estimated the amount of StarLink corn that may have entered the human food supply, based on a grower survey performed in 1999 for Aventis. This survey asked a random sample of growers how they had handled their StarLink grain. The results indicated that between 60% and 99% of growers directed their StarLink grain only to animal feed or ethanol uses. The range in predicted compliance reflects the significant percentage of respondents who answered, in effect, either "Don't Know" or "Undecided."

Thus, EPA calculated potential mixing as follows:

3. Total Bushels of StarLink Corn produced in 1999 (1999 StarLink): 44 million

4. Assuming 60% compliance and that 10% of Starlink grain is consumed on farm,
Total bushels consumed on farm (10%): 4.4 million
Total bushels sent to animal feed or ethanol (50%): 22 million
Total bushels entering human food supply (40%): 17.6 million

5. Assuming 99% compliance and that 10% of Starlink grain is consumed on farm,
Total bushels consumed on farm (10%): 4.4 million
Total bushels sent to animal feed or ethanol (89%): 39.2 million
Total bushels entering human food supply (1%): 0.4 million

6. Assuming that StarLink grain is mixed with non-Starlink grain in an average ratio of 1:30,
Total bushels of co-mingled StarLink and non-StarLink grain in animal feed or ethanol
For 60% compliance (31 x 22 million): 682 million bushels
For 99% compliance (31 x 39.2 million): 1,215 million bushels

7. Percentage Mixing for 60% Compliance Scenario
Total Bushels US Field Corn Production: 9.4 billion = 9,400 million
Subtracting 10% grain assumed to be consumed on farm: 940 million bushels,
Subtracting 682 million bushels in animal feed (see step 6)
Leaves 7,778 million bushels of which 17.6 million could be StarLink or 0.23%
(This calculation assumes that StarLink corn not directed to animal feed or industrial uses is completed co-mingled with all available non-StarLink grain prior to some portion of the co-mingled grain entering the human food supply.)

8. Percentage Mixing for 99% Compliance Scenario
Total Bushels US Field Corn Production: 9.4 billion = 9,400 million
Subtracting 10% grain assumed to be consumed on farm: 940 million bushels,
Subtracting 1,215 million bushels in animal feed (see step 6)
Leaves 7,245 million bushels of which 0.4 million could be StarLink or 0.006%
(This calculation assumes that StarLink corn not directed to animal feed or industrial uses is completed co-mingled with all available non-StarLink grain prior to some portion of the co-mingled grain entering the human food supply.)

REFERENCES

Brassard, D. (2000). BEAD's Review of Novigen's Safety Assessment of StarLink. USEPA Memorandum. 11 pp.

Evans, D.F., Pye, G., Bramley, R., Clark, A.G., Dyson, T.J., and Hardcastle, J.D. (1988). Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 29:1035-1041.

Fallingborg, I. (1999). Intraluminal pH of the human gastrointestinal tract. *Danish Medical Bulletin* 46(3):183-193).

Fallingborg, J. Christensen, L.A., Ingeman-Nielsen, M., Jacobsen, B.A., Abildgaard, K., Rasmussen, H.H., and Rasmussen, S.N. (1990). Measurement of gastrointestinal pH and regional transit times in normal children. *Journal of Pediatric Gastroenterology and Nutrition* 11(2):211-214.

Russell, T.L., Beradi, R.R., Barnett, J.L., Dermentzoglou, L.C., Jarvenpaa, K.M., Schmaltz, S.P., and Dressman, J.B. (1993). Upper gastrointestinal pH in seventy-nine healthy, elderly, North American men and women. *Pharmaceutical Research* 10(2):187-196.