January 19, 2005

By Regular Mail
Division of Dockets Management [HFA-305]
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20853

Re: Comments on Food and Drug Administration Docket No. 2004D-0369

The Center for Science in the Public Interest ("CSPI")[1] hereby submits comments to the Food and Drug Administration ("FDA") on its "Draft Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use," published in the Federal Register on November 24, 2004 (69 FR 68381) (hereinafter referred to as "Draft Guidance"). That Draft Guidance sets forth a process for a voluntary early food safety evaluation of plant varieties with new proteins to ensure that if intermittent, low-levels of those proteins are found in the food supply, they will not be harmful to humans or animals.

CSPI commends FDA for acknowledging that experimental food crops engineered with new proteins could end up in the food supply and present risks to humans and animals. Unfortunately, FDA's solution to this problem as set forth in the Draft Guidance does not adequately ensure the safety of the food supply. To achieve a federal policy that safeguards the food supply, the Draft Guidance needs to have a broader scope than currently proposed. The

[1] CSPI is a nonprofit education and advocacy organization that focuses on improving the safety and nutritional quality of our food supply and on reducing the damage caused by alcoholic beverages. CSPI seeks to promote health through educating the public about nutrition and alcohol; it represents citizens' interests before legislative, regulatory, and judicial bodies; and it works to ensure advances in science are used for the public good. CSPI is supported by the 850,000 member-subscribers to its Nutrition Action Healthletter and by foundation grants. CSPI receives no funding from industry or the federal government.

Draft Guidance should cover any engineered food crop, regardless of the crop's intended purpose. In addition, the early food safety assessments should be mandatory and assess every engineered crop, even if the same protein has already been introduced into another crop. Finally, the response that FDA generates after completing the early food safety evaluation should affirmatively state that FDA believes the new protein presents no new food safety risks to humans or animals.

In response to FDA's Federal Register notice, CSPI provides the following comments on how FDA can improve its Draft Guidance:

I. The Proposed Voluntary Evaluation System Will Not Protect Human Health.

The Draft Guidance sets up a procedure that encourages, but does not require, developers of plant varieties with new proteins to submit certain safety data for an early review in case small amounts of that product inadvertently end up in the food supply. Thus, the procedures set forth in the Draft Guidance rely on the sponsors to voluntarily subject their crops to FDA review instead of FDA mandating that all new proteins be assessed and approved before further plantings are allowed. Only a mandatory review and approval process, however, will adequately protect the food supply and consumers.

CSPI commends FDA for acknowledging that experimental plants could inadvertently enter the food supply and for proposing an early food safety assessment for such crops. To truly protect human health and the integrity of the food supply, however, any new substance that could get into the food supply should have a mandatory food safety assessment. Genetic engineering is a relatively new technology for producing food and one cannot currently predict what products will be produced and whether they will be safe. A mandatory review of new proteins engineered into food crops will reduce the likelihood that a new protein from a engineered plant variety could have a harmful effect on humans. Such a mandatory review will also bolster public confidence in both genetically engineered foods and the government's regulation of those foods. Finally, plant varieties with new proteins cannot be released into the environment without review and approval by the US Department of Agriculture ("USDA") and/or the Environmental Protection Agency ("EPA"). If any potential concern about the environmental effects of plant varieties with new proteins requires a mandatory federal approval by USDA and/or EPA, then any potential food safety concerns about those same products deserve a similar mandatory review and approval at FDA. Therefore, FDA needs to mandate the early food safety assessments.

II. The Scope of the Draft Guidance is Too Narrow.

The Draft Guidance states that it only cover "new plant varieties that are intended for food use." That scope is too narrow because it excludes biotechnology-derived food crops that have been engineered to produce non-food substances, such as pharmaceuticals, industrial chemicals or other protein substances. The trigger for whether a early food safety evaluation is conducted should not be the "intent" of the sponsor, but instead should be whether a crop that is

eaten by humans or animals contains a new protein.

The Draft Guidance seeks to address the fact that "cross-pollination due to pollen drift from field tests to commercial fields and commingling of seeds produced during field tests with commercial seeds or grain" could result in the "inadvertent, intermittent, low-level presence in the food supply" of new proteins that have not been evaluated for food safety. Hundreds of field tests using food crops engineered to produce non-food substances have occurred and will continue to occur in the future. Those crops have a similar likelihood of entering the food supply through cross-pollination or commingling as crops engineered for food use. Therefore, all engineered food crops, irrespective of their intended use, should be included in the scope of the Draft Guidance. As currently written, the Draft Guidance only covers a small part of the potential contamination problem it is attempting to address.

III. The Draft Guidance Should Clearly Define When the Early Food Safety Evaluation Process is to Begin.

For the early food safety evaluations to be helpful in safeguarding the food supply from new proteins with food safety concerns, the time when the evaluation is done is critical. The Draft Guidance is ambiguous, however, about when a sponsor should send in an early food safety evaluation submission to FDA. On page 6 of the Draft Guidance, it states that FDA recommends beginning the process "prior to the stage of development where the new protein might inadvertently enter the food supply." Then on page 7, the Draft Guidance states that the sponsor submit the evaluation "prior to the time you [the sponsor] have concerns that the new protein could enter the food supply, for example via pollen flow or commingling as you increase the size or extent of field testing." Both those statements are extremely vague and provide no objective criteria for when a submission is expected. Instead, they leave the decision about when a crop might have an impact upon the food supply solely up to the discretion of the sponsor.

The critical decision about when to conduct the early food safety evaluation should not be left up to the sponsor. Thus, the FDA Draft Guidance should set forth a clear test for when the submission is expected with enough examples so that there is no ambiguity about when the process should begin. Several potential triggers for when an early food safety evaluation should be conducted might be (1) when the trial reaches a certain acreage (e.g. five acres), (2) after a certain number of outdoor plantings of the crop (e.g. after the third planting), or (3) when the experimental field trial no longer addresses proof of concept but begins to collect biosafety or agronomic data.[2]

[2] CSPI believes the discussion about whether developers might chose to complete a early food safety evaluation in the "Information Collection Burden Estimate" portion of the federal register notice does not set forth examples consistent with the Draft Guidance. Uncertainty about the future viability of a crop should not be used as a factor in determining whether to conduct a safety evaluation. Similarly, the developer's judgment about the effectiveness of the containment measures should not determine whether to conduct a safety evaluation. There are several examples (e.g. Prodigene) where a developer believed they were in compliance with containment

IV. The Early Food Safety Evaluation Process Should be Completely Transparent and All Relevant Documents Should be Made Available on the Internet.

It is extremely important that FDA take every possible action to make the early food safety evaluation process as transparent as possible. This includes making all relevant documents available to the public in a timely and easily accessible fashion.[3] When feasible, all documents should be put onto the Internet, which would allow easier access for people interested in the documents but who are not physically located in the Washington, DC area.

CSPI applauds FDA for stating that it will make available to the public via the Internet both the early food safety submission from the sponsor and the response letter issued by FDA. It is unclear, however, why FDA has not stated that it will treat other documents relevant to the early food safety evaluation process in the same manner. All documents contained in the administrative file should be publicly available, including all correspondence between the sponsor and FDA, all materials provided by the sponsor, and any documentation of meetings regarding the new protein. Making all documents relevant to the submission available will increase the transparency of FDA's evaluation process and ensure that the public has access to the same information about the new protein that is available to FDA.

Although the Draft Guidance states that the submission and FDA's response will be made public, it does not specify **when** those documents will be put on the Internet. If FDA's process is to be truly transparent, all relevant documents need to be made public as soon as possible after they have been received or generated by FDA. In particular, the sponsor's submissions should be put on the Internet no later than 30 days after receipt by FDA and well in advance of FDA's response. Similarly, FDA response to the company should be made available to the public simultaneous with its receipt by the sponsor. Providing documents as they are received or generated will allow the public to follow the early food safety evaluation process as it progresses to completion instead of only reading about it as an after-the-fact historical record.

V. The Public Should be Allowed to Participate in the Early Food Safety Evaluation Process.

The proposed early food safety evaluation process should invite the public to submit comments on a sponsor's submission or the new protein at any point during the 120-day review. The purpose of the early food safety evaluation is to ensure that if a new protein makes its way into the food supply in small quantities, it will not harm humans or animals. Clearly, ALL

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measures and yet an experimental crop ended up contaminating part of the food supply.

[3] CSPI understands that some documents submitted by the sponsor may contain legitimate confidential business information that cannot be released to the public. If a sponsor wishes to make such a claim for any portion of its submissions, it should be made at the time of the submission and be supported with documentation that shows the claim satisfies the legal standard. FDA should review and determine the legitimacy of the claim in an expedited fashion and make available to the public any information that does not meet the legal requirements.

relevant data on the allergenicity or toxicity of the new protein would be helpful to FDA's review of the genetically engineered food, not just information from the sponsor. Therefore, FDA should allow for the submission of information by the public relevant to the FDA review of the genetically engineered food.

To allow adequate public participation, FDA should (1) publish in the Federal Register a notification identifying that it has received a submission from a sponsor, (2) make the company's submission available on the Internet, (3) allow the public at least 30 days to provide comments and information, and (4) review any public comments before finalizing its response to the sponsor. Such a process should be easy to complete within the 120-day response period set forth in the Draft Guidance.

VI. The FDA Response Should Affirmatively State Whether FDA Believes the New Protein Raises Food Safety Concerns.

FDA should conclude the early food safety evaluation of any new protein with an affirmative statement about whether the new protein raises any food safety concerns or is as safe as its conventional counterpart. An affirmative statement would be much more helpful to the sponsor and the public than a statement that the agency does not have any questions regarding the notifier's view that the food is safe. If FDA will not publicly state its opinion on the safety of the new protein, at a minimum, FDA's response should set forth in detail the basis for FDA's conclusion that it has no questions at this time about the sponsor's assessment of the product.

VII. Field Testing Should Not Continue Until the Early Food Safety Assessment Has Been Completed.

The Draft Guidance states that the early food safety evaluation should occur when the new protein "could enter the food supply, for example via pollen flow or commingling as you increase the size or extent of field testing." To prevent unsafe proteins from being found in commercial seed, commodities, or food/feed, sponsors should not be allowed to continue field testing until FDA completes their early assessment. Without such a prohibition, the very activity that the Draft Guidance is attempting to prevent (unsafe proteins getting into our food) may occur while the FDA assessment is being completed.

VIII. The Proteins to be Reviewed Under the Draft Guidance are Too Narrow.

The Draft Guidance states that FDA does not expect to receive an early food safety evaluation if the protein already has been evaluated either in a biotechnology consultation or a previous early food safety evaluation, even if the protein is being introduced into a different plant species. The unstated reason for that exemption is that the allergenicity and toxicity assessment for a new protein would be identical in subsequent submissions. In addition, the Draft Guidance also states that it does not expect submissions for native proteins moved within the same species, unless the protein is being produced at a "significantly elevated level." The unstated reason for

that exemption is that the engineered protein would raise no new food safety concerns since it comes from a crop that humans already eat. The scientific reasoning for both exemptions, however, is incorrect. Both identified categories of proteins should not be exempt from FDA's early food safety assessment because both situations can result in the introduction of an allergen or toxin into the food supply.

The introduction of the same gene from the same source in two different plants (such as corn and wheat) could raise different concerns about toxicity and allergenicity. Expression levels could be different in different species (or even in different varieties of the same species) and both toxicity and allergenicity are dose dependent. Also, how a food is processed for human consumption (e.g. eaten raw versus cooked or milled) and the amount of the food in a person's diet can affect exposure. Processing may destroy or alter the protein, eliminating or changing toxicity or allergenicity. Exposure to a protein at very low levels might not cause a toxic or allergenic reaction but exposure at higher levels might elicit a negative response. Thus, a protein engineered into a corn plant might not be toxic but the same conclusion might not be true for expression of that same protein in an apple or a different corn plant.

Similarly, moving a gene within the same species also can raise toxicity or allergenicity concerns. Some proteins in food crops may only be expressed in non-edible portions of that crop. If one of those proteins is moved to the edible portion, humans would be exposed to a new protein that might result in a toxic or allergenic reaction.[4] To avoid that possibility, even genes being moved within a species should have an early food safety assessment to rule out any human health concerns.

CSPI appreciates this opportunity to submit comments on FDA Draft Guidance. If FDA would like additional information from CSPI about these comments, we would be happy to meet with you at your convenience.

Sincerely,

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[4] According to the Draft Guidance, moving a gene's expression from a non-edible portion of the crop to an edible portion would not trigger an early food safety evaluation unless the protein was expressed in "significantly elevated levels." The same level of expression in the edible portion as in the inedible portion, however, could still result in an allergenic or toxic risk.