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January 24, 2005

[Hand Delivered]

Mr. Jeffrey Shuren  
Assistant Commissioner for Policy  
Divisions of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

Re: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use (Docket No. 2004D-0369)

Dear Mr. Shuren:

Monsanto Company is a leading provider of agricultural solutions to growers worldwide. Monsanto's 12,000 employees provide top-quality, cost-effective and integrated approaches to help farmers improve their productivity and produce better quality foods.

On Nov. 24th, 2004, the Food and Drug Administration published in the Federal Register a request for public comments on draft guidance for industry entitled "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use" (69 FR 68381). Monsanto is providing this response to that request.

The Food and Drug Administration (FDA), the Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) regulate biotechnology-derived products through the Coordinated Framework. The Coordinated Framework has been effective and successful in assuring the food, feed and environmental safety of the products developed using modern biotechnology. Regulations developed by the US Regulatory Agencies as part of the Coordinated Framework have consistently been based on sound science, with the intent of fostering the expansion of new technology, while maintaining the highest standards of health and environmental safety. In August 2002, the Office of Science and Technology Policy (OSTP) proposed federal actions to update field test requirements and to establish early voluntary food safety evaluations for new proteins produced by biotechnology-derived plants<sup>1</sup>. Monsanto endorsed the principles and proposed federal actions outlined in that proposal. We believe that a science-based, coordinated approach to early food safety evaluation and field testing standards is the most effective way to assure food safety and to provide certainty, confidence and acceptance in the development and regulation of biotechnology-derived crops intended

<sup>1</sup> 67 FR 50578-50580

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for food or feed use. Therefore, we support the current draft guidance from FDA as the first step in implementing the OSTP proposed federal actions.

We encourage FDA to continue its efforts and work in close cooperation with other federal agencies to develop sound regulatory policies related to the field testing and evaluation of these products and to fully implement the OSTP policy. Additionally, we remain committed to meeting or exceeding the confinement measures established by USDA and EPA.

The key underpinning of the proposal for early food safety evaluation is the well-established FDA food safety approach that recognizes that the information required to establish safety is based principally on exposure and hazard. We support the focus on the toxicity and allergenicity potential for new, unfamiliar proteins given that since regulated field trials are planted under confinement provisions, exposure will be rare and at very low levels. Hence, there is no rationale to consider other components of the food, such as nutrients or anti-nutrients, due to negligible exposure. We also support the concept of exemptions from the requirement of an early safety evaluation based on the agencies' familiarity with the encoded protein or a lack of new exposure. As noted in the OSTP policy, familiar proteins would include those previously assessed for safety in any crop and native proteins and we support FDA's decision that multiple submissions would not be expected for the same protein from the same source gene or for proteins moved within the same species.

As the guidance document will serve as a key element of the U.S. policy related to the early food safety evaluation of biotechnology-derived plants, we encourage FDA to clearly describe the scientific basis for the decision to focus the evaluation on the expressed protein product in the final guidance document. This description would explain that the other factors considered necessary for a full assessment for commercial release, such as potential compositional or nutritional changes, are not necessary since any such changes would be diluted to a level that does not raise a safety or nutritional concern as any products from biotechnology-derived plants covered under this early safety evaluation would be present at negligible levels, if at all.

In the draft guidance, FDA recommended the inclusion of six specific types of data related to the potential toxicity or allergenicity of the new protein in the synopsis of the safety data and information for the Early Food Safety Evaluation. FDA further references specific paragraphs of the Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived From Recombinant-DNA Plants for additional guidance. Monsanto believes that these data and the guidance provided under the Codex Guideline are appropriate to conduct and complete the early safety evaluation. Additional information regarding composition would, of course, be provided when the developer completes the consultation process, but the protein evaluation would not need to be repeated.

FDA previously stated that they would not expect to conduct early food safety evaluations for proteins moved within the same species, as such movement would not

raise new toxicity or allergenicity issues for the food<sup>2</sup>. In this guidance document, however, FDA recommended that a native protein that has been produced at a significantly elevated level in the final product be evaluated under the early food safety process. This recommendation seems inconsistent with the previously stated principle that the potential incidental, low level presence of the biotechnology-derived food would not create a new exposure nor result in a high level of exposure. Even a significant elevation (100 – 1000-fold increase) in the level of a native protein would not result in a significant increase in exposure, since the same principles of dilution would apply. Thus, elevated levels of native proteins should not necessitate an early food safety evaluation.

FDA has proposed establishing a list on its website of all proteins it has evaluated and considered acceptable through the early food safety evaluation. We suggest that the list include proteins previously reviewed in FDA's consultation process and, in addition, be developed in close cooperation with EPA so that all proteins that have been determined to pose no safety concern would be listed in a single location.

In Section V of the draft guidance, FDA provided a series of questions and answers related to communication between FDA and the developer. In Section V.C, FDA stated that they will make the information in the submission easily accessible to the public via the Internet and in Section V.B, FDA noted that any information that is publicly available could be utilized by someone other than the developer. While Monsanto is supportive of transparency at the appropriate steps in the regulatory process, we have several concerns about these statements in relation to the early food safety evaluation. First, by its very nature, an early food safety evaluation will be prepared for a protein that is in the development phase and there will likely be instances when the developer wishes to retain the identity of the protein as confidential until, for example, a patent application is filed or issued. This information is often claimed as confidential business information in USDA field trial notifications / permits since its disclosure could provide a rich source of information to competitors. In such instances USDA publicly discloses only the phenotype, not the specific protein. We request that the Agency include a similar option for listing the protein. This listing could be updated as the protein moves from the development to the pre-commercial stage.

Second, FDA stated that the contents of the submission will also be posted on the Internet. One type of information required for the early evaluation is an assessment of the amino acid sequence of the protein compared to known allergens and toxins, which again could provide information to competitors if it were not able to be protected on a case-by-case basis. Lastly, if FDA posts the information provided by the developer on the Internet, it would by definition be considered public and therefore could be utilized by others. Because the data and information provided as part of an early safety evaluation would be on the protein itself and not on a specific transformation event, the information could potentially be used by others who are developing products that produce the same protein. We believe that developers will be concerned about the potential to disclose important competitive information and therefore be discouraged from participating in the early safety evaluation process. We request that FDA address these

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<sup>2</sup> *ibid.*

concerns about the confidentiality and use of the data when considering the type of information that they will make available via the Internet. We further encourage FDA to strengthen their regulations consistent with applicable law to protect confidential business and trade secret information by providing for exclusive use and/or protection of the data submitted by the developer.

In Section VII of the draft guidance document, FDA proposed to add submissions to their “inventory” of early food safety evaluations within 15 days of receipt if the submission appears to include all of the recommended elements. It is not clear whether the “inventory” refers to the queue for review, the administrative file, or posting on the Internet. Monsanto encourages FDA to post both the submission and response letter, consistent with confidentiality requirements, upon completion of the early food safety evaluation.

We encourage FDA and the U.S. government to continue their dialogue and cooperation with governments around the world to assure consistent science-based regulations. These discussions should address regulatory processes to establish the safety of biotechnology products that might be present at intermittent, low levels in commercial seed, commodities or food/feed. This is a high priority for products that are fully approved and commercial in the U.S., but may be awaiting domestic approval in the country of import. We believe that the principles established by OSTP and in this science-based policy guidance will be a useful reference in these discussions.

Of course, implementing the guidance and appropriately incorporating it into policy discussions must be supported by adequate agency resources that are sufficient to develop, administer, and continue dialogue with other agencies, governments and intergovernmental organizations. We urge FDA to devote the funds and personnel necessary to appropriately support these initiatives.

In summary, Monsanto believes that a science-based, coordinated approach to early food safety evaluation and field testing standards is the most effective way to assure food safety and provide more certainty, confidence, and acceptance in the development and regulation of biotechnology-derived crops intended for food or feed use. We appreciate this opportunity to provide comments to FDA’s draft guidance and encourage its rapid finalization.

Sincerely,

A handwritten signature in black ink, appearing to read "Marsha A. Stanton". The signature is fluid and cursive, with a long horizontal stroke at the end.

Marsha A. Stanton, Ph.D.  
Director, Seed Regulatory Policy