

Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins
Produced by New Plant Varieties Intended for Food Use

SUPPORTING STATEMENT

A. Justification

1. Circumstances Necessitating Information Collection

The use of bioengineered plants for food production in the United States has increased markedly over the past decade (food refers to both human food and animal feed). As the number and diversity of field tests for bioengineered plants increases, the likelihood of cross-pollination occurring due to pollen drift from field tests to commercial fields and commingling of seeds produced during field tests with commercial seeds or grain may also increase. This could result in the inadvertent, intermittent, low-level presence in the food supply of a protein that has not been evaluated in the U.S. Food and Drug Administration's (FDA) biotechnology consultation process.¹

FDA first addressed the safety evaluation of new proteins in bioengineered plants in its 1992 Statement of Policy: Foods Derived from New Plant Varieties ("1992 policy;" 57 FR 22984, May 29, 1992) (available at <http://www.cfsan.fda.gov/~acrobat/fr920529.pdf>). Since FDA first issued its 1992 policy, the agency has encouraged developers of new plant varieties, including those varieties developed through biotechnology, to consult with FDA early in the development process to discuss possible scientific and regulatory issues that might arise. In a notice in the Federal Register of August 2, 2002 (67 FR 50578), the U.S. 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 bioengineered plants ("the OSTP document").

On November 24, 2004, FDA announced in the Federal Register (69 FR 68381) the availability of a draft guidance for industry entitled, "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use" ("the New Protein Guidance") (draft guidance available at <http://www.cfsan.fda.gov/~dms/bioprgui.html>). The draft guidance provides recommendations to developers of new plant varieties, in particular bioengineered plants, on the early food safety evaluation of new non-pesticidal proteins and on the procedures for submitting an early food safety evaluation of such proteins to the agency.

FDA is requesting OMB approval of the voluntary information collection provisions contained in the New Protein Guidance. The recommendations put forward in the New Protein Guidance are consistent with the scientific principles articulated in the 1992 policy for food safety evaluation of a new protein. The guidance continues to foster early

¹ The document entitled, "Guidance on Consultation Procedures: Foods Derived from New Plant Varieties," can be found at <http://www.cfsan.fda.gov/~lrd/consulpr.html>.

communication by encouraging developers to submit to FDA their evaluation of the food safety of their new protein. Such communication helps to ensure that any potential food safety issues regarding a new protein in a new plant variety are resolved early in development, prior to any possible inadvertent introduction into the food supply of material from that plant variety. Submission of an early food safety evaluation for a new protein is not meant to substitute for a biotechnology consultation with FDA about a food derived from a new bioengineered plant variety. A developer may use the information developed for the early food safety evaluation of a new protein in the biotechnology consultation process.

2. How, By Whom, Purpose of Collection

This is a new information collection. The New Protein Guidance is for developers of new plant varieties that are intended for food use. This guidance provides information and recommended procedures for a scientific evaluation of the food safety of new proteins produced by such new plant varieties. This guidance also provides information to developers about consulting with FDA about their evaluation and recommended procedures for submitting an early food safety evaluation of such proteins to the agency.

The recommended procedures contained in the New Protein Guidance are voluntary. Developers of new plant varieties will conduct the scientific evaluation and submit it to the agency. There has been particular interest within the U.S. government and the food and agriculture industries in having FDA publish this guidance. That interest stems in part from concerns that, some day, material from bioengineered food crops undergoing field trials might inadvertently enter the food supply without any prior food safety evaluation. While FDA has not found and does not believe that new plant varieties under development for food and feed use generally pose any safety or regulatory concerns, this guidance is consistent with FDA's policy of encouraging communication early in the development process for a new plant variety. Such communication helps to ensure that any potential food safety issues regarding a new protein in such a new plant variety are resolved prior to any possible inadvertent introduction into the food supply of material from that plant variety.

FDA is the primary user of the information to be disclosed. However, as noted above, a developer may use the information developed for the early food safety evaluation of a new protein in the biotechnology consultation process. In addition, the public may use this information. In FDA's experience, there has been a considerable interest from a broad segment of the public, including members of the regulated industry, other federal, state, and local government agencies, international government agencies, and public interest groups, in bioengineered plants. FDA plans to assign a number to each submission and create a list of the submissions for posting on the Internet. The information on the Internet will include a hyperlink to the text of each submission (other than confidential commercial information) and a hyperlink to the text of the letter issued by the agency in response to each submission. This information will be easily accessible to the public on FDA's Internet site.

3. Consideration Given to Information Technology

The new protein guidance does not specifically prescribe the use of automated, electronic, mechanical, or other technological techniques or other forms of information technology as necessary for use by developers. Developers are free to use whatever forms of information technology may best assist them in voluntarily conducting the scientific evaluation and submitting it to the agency. Information for early food safety evaluations may be collected electronically. If the evaluation is submitted to FDA as an electronic file, one paper copy is also requested.

4. Identification of Duplicative Information

FDA plans to avoid duplicative collection of this information. If a protein has been evaluated in an early food safety evaluation and no safety concerns are identified, we would not expect an additional early food safety evaluation to be submitted if the same protein is introduced into another plant species. Also, if a protein has previously been reviewed as part of a biotechnology consultation and there were no safety concerns identified, we would not expect the submission of an early food safety evaluation for such a protein.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 et seq.), the U.S. Environmental Protection Agency (EPA) has authority to regulate all pesticides, regardless of how they are made or their mode of action. Thus, a plant bioengineered to contain a pesticide will also be reviewed by EPA. No person may sell or distribute a pesticide in the United States that is not registered, except under certain circumstances; EPA also has the authority to regulate unregistered pesticides, e.g., in field testing. EPA can establish conditions for use as part of the registration and for uses of unregistered pesticides. The EPA also sets tolerance limits for residues of pesticides on and in food and animal feed, or establishes an exemption from the requirement for a tolerance, under the Federal Food, Drug and Cosmetic Act (FFDCA; the act). Under the FFDCA, FDA has authority to regulate a non-pesticidal substance that may be introduced into a new plant variety and that is expected to become a component of food. This early food safety evaluation guidance applies to non-pesticidal proteins and is not duplicative with EPA responsibilities.

Many plants developed using recombinant DNA (rDNA) technology are considered "regulated articles" under regulations of USDA's Animal and Plant Health Inspection Service (APHIS) (7 CFR Part 340), which regulates the introduction of certain "genetically engineered" plants into the environment. A developer must obtain authorization from APHIS to field test such crops and, depending on the nature of the crop, a developer files either a permit application or a notification. A developer's submission to APHIS includes information on the plant from which the food is derived, and details of the genetic changes to the plant. APHIS considers issues of agricultural and environmental safety during field trials, such as whether the crop could cause harm to

plants or plant products, non-target organisms, or threatened and endangered species. After a period of research and development to gather safety data, a developer may request that APHIS grant “non-regulated” status to the genetically engineered plant, meaning that the agency has determined that the plant is as safe as similar conventionally bred varieties and as such will no longer be subject to APHIS oversight. In contrast, FDA requests a submission of data and information concerning the food safety of a specific new protein produced in a new plant variety. Therefore, although a submission to APHIS would include some information, such as the name of the company and the identity of the protein, that would be included in the information requested under FDA’s guidance for the early food safety evaluation of new proteins, the submission is not duplicative.

5. Small Businesses

In the guidance, the agency has established criteria as to the type of information necessary for these submissions. The New Protein Guidance minimizes the reporting burden on all businesses, including small businesses, by providing that the developer submit a summary of data and information, rather than the data and information itself. There is no known way to minimize the burdens on a small business wishing to submit a request for action to the agency.

Further, submitting an early food safety evaluation to the agency for comment is voluntary. There would not be additional burden to the developer for developing the data and information that underlie the new protein evaluation because they would have already generated such data and information to insure that the protein is safe and is in compliance with all applicable requirements of the FFDCA.

6. Less Frequent Information Collection

FDA believes that this current evaluation reinforces statutory requirements for foods to be safe, including foods derived from biotechnology. The New Protein Guidance encourages earlier consultation with FDA prior to the time that a new protein could enter the food supply, thus ensuring that no safety issues would be raised by the possible presence of such a protein in the food supply. This information collection makes FDA more aware of new proteins that could enter the food supply at low levels and gives the public more confidence in the safety of their food. Further, as noted above, submitting an early food safety evaluation to the agency for comment is voluntary.

7. Information Collection Circumstances

Allowing developers to submit an early food safety evaluation to the agency for comment does not involve submission of information more than quarterly to the agency, written responses to the agency in less than 30 days, submission of multiple copies, retention of records for more than three years, or the use of statistical methods.

With regard to the confidentiality of the information or the submission of trade secrets or proprietary information, the agency expects that it may receive submissions containing

confidential commercial information. FDA will handle information submitted as part of a food safety evaluation of a new protein in accord with the requirements of the Freedom of Information Act, other applicable statutes, and FDA's regulations at 21 CFR Part 20. Consistent with confidentiality requirements, FDA will make submissions of early food safety evaluations for new proteins, and FDA's responses thereto, easily accessible to the public via the Internet. FDA believes this is consistent with the goal, as articulated in the OSTP document, of enhancing public confidence in the regulatory oversight of bioengineered plants.

8. Consultations with Persons Outside the FDA

In the Federal Register of November 24, 2004 (69 FR 68381), FDA published a Notice of Availability with a 60-day notice requesting public comment on the collection of information in FDA's draft guidance document titled, "Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use."

Nonresponsive comments

FDA received approximately 5000 letters in response to the Notice. However, many of these letters contained comments that were not responsive to the PRA questions. For example, several comments expressed the opinion that the collection of information was insufficient to ensure safety; other comments expressed concern that the agency might not be able to commit sufficient resources to performing early food safety reviews without having to redirect resources from other tasks; that the decision should not be left to the developer regarding when to submit an early food safety evaluation to the agency; and about the objectivity and scientific expertise of the individuals reviewing the information.

(Response) These comments are general comments directed to the adequacy of the guidance, rather than specific comments relevant to the collection of information; therefore, these non-responsive comments will not be addressed in this document.

Responsive comments

FDA received several letters with specific comments responsive to the comment request concerning the proposed information collection in the notice. The comments and FDA's responses follow.

(Comment 1) Several comments were supportive of the information collection, stating that the information collection was necessary for FDA to fulfill statutory requirements to protect the safety of the food supply. Relevant to the minimization of burden, several of these comments also noted that the information collection was appropriately limited in scope to prevent duplicative submissions among federal agencies.

(Response) These comments provide support for the utility of the information collection and confirm that the collection will not result in a duplicative information collection among federal agencies.

(Comment 2) One comment suggested that FDA should minimize the burden on developers by referencing in the guidance the availability of public protein databases that could be useful in the evaluation of allergen or toxin homology.

(Response) FDA does not want to reference or list the various databases because to do so would imply that FDA is endorsing any or all of them. FDA finds that there are several databases in the public domain that are easily obtained through the internet, are known in the scientific community, and are in common use by developers of bioengineered crops.

(Comment 3) One comment suggested that FDA could minimize the burden of the proposed collection of information by clarifying that a weight of the evidence approach is applied to the assessment of potential allergenicity of a new protein. The comment further suggested that alternative methods and protocols be considered in the evaluation of the allergenicity of new proteins.

(Response) FDA's guidance does not state that a weight of the evidence approach will be applied to the evaluation. The guidance describes a case-by-case evaluation that recognizes that different pieces of information may have varying importance for the food safety evaluation depending on the characteristics of the protein. As stated in the guidance, developers are free to use alternative approaches in their evaluations. The comment fails to explain how a weight of the evidence approach would reduce the burden under the PRA.

(Comment 4) One comment suggested as an approach to minimize burden on developers that FDA treat highly similar proteins as a family of proteins, if they differ only by a few amino acids but retain the same function, rather than evaluating each protein individually, though the comment further suggests that certain aspects of a protein may be evaluated individually.

(Response) FDA notes that the guidance is intended to consider specific proteins, not protein families. FDA further notes that even small changes in amino acid sequence may alter a protein and these small differences could also have implications for food safety. However, if there is relevant information contained in a previous submission, that information can be incorporated by reference into a current submission for a new protein evaluation.

(Comment 5) One comment suggested as a means of minimizing burden of the proposed collection of information that FDA provide standard forms or formats for certain elements of the submission (e.g., bioinformatics reports). The comment also suggested minimizing burden by making greater use of electronic submissions.

(Response) FDA has considered the use of standardized forms or formats and at this time does not believe that their use would reduce the burden of the information collection. The use of standardized forms could discourage alternative approaches for the presentation of data in an evaluation that might more clearly or thoroughly set forth the data. Developers will have access to the forms and formats used by previous submitters and are free to use them; thus, at this time we do not perceive a need for a standardized form. Based on its experience in evaluation of submissions FDA will in the future revisit whether the use of standardized forms and formats would be advantageous to developers.

With respect to electronic submissions, FDA states in the guidance that electronic submissions are acceptable, but one paper copy is also requested. Efforts are underway at FDA to convert in the future to a submission process that is entirely electronic.

(Comment 6) One comment stated that a way to enhance the quality, utility, and clarity of the information to be collected is to follow guidance available from the Codex

Alimentarius. Although the comment did not specify which guidance from the Codex Alimentarius FDA should follow, FDA believes that the comment is referring to the Codex Alimentarius “Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants” (CAC/GL 45-2003) (the Codex Plant Guideline), containing “Annex: Assessment of Possible Allergenicity” (the Codex Allergenicity Annex). The comment also stated that FDA should make Codex guidance a mandatory part of its guidance.

(Response) FDA agrees in part and disagrees in part. FDA notes that its recommendations in this guidance are consistent with the approach recommended in the Codex Plant Guideline. In fact, FDA references the Codex Plant Guideline as a resource to be consulted by a developer in evaluating the food safety of a new protein. However, FDA notes that the Codex Plant Guideline addresses a broad range of issues associated with food safety assessment of food derived from bioengineered plants. While FDA’s guidance is consistent with the Codex Plant Guideline, it does not address the entire broad range of issues as that document. FDA’s guidance is focused on the food safety issues that might arise from the intermittent, low-level presence of material from a plant being developed for food and feed use. FDA believes that any potential risk from the intermittent, low-level presence of such material in the food supply would be limited to the food safety of the new proteins. FDA references the Codex Plant Guideline, Paragraphs 34-43 under *Expressed Substances (non-nucleic acid substances)* and the Codex Allergenicity Annex, for that component of the safety review.

FDA disagrees with the comment’s suggestion that the agency make the Codex Plant Guideline a mandatory part of its guidance. While FDA believes that the Codex Plant Guideline and the Codex Allergenicity Annex are useful documents, it recognizes that other approaches may also be appropriate.

(Comment 7) One comment stated that while the information to be collected is essential and important for FDA to obtain, the information is inadequate to fulfill FDA’s “stated and mandated goals,” and therefore it is of questionable utility.

(Response) FDA disagrees. The guidance is properly focused on the food safety assessment of a new protein produced in a new plant variety when there might be a low-level, intermittent presence of material from a plant being developed for food. Although the commenter would like more information to be presented for FDA review at this stage, FDA notes that more information is not necessary because the information that the guidance recommends a developer collect and present to FDA as part of a food safety evaluation of a protein is adequate for the specific assessment that FDA is making at this stage. FDA recommends that a broader scope of information be presented to FDA for review at subsequent evaluation stages. For example, when a developer utilizes the recommendations articulated in FDA’s guidance entitled, “Consultation Procedures for New Plant Varieties” (available at <http://www.cfsan.fda.gov/~lrd/consulpr.html>), FDA expects that significantly more information will be presented during the consultation.

(Comment 8) Several comments challenged the accuracy of FDA’s estimate of the burden of the proposed collection of information. These comments opined that FDA should collect more extensive information than what is proposed in the guidance and they concluded, therefore, that FDA had underestimated the burden of the proposed

information collection. The comments did not challenge the accuracy of the burden estimate for the information as proposed in the guidance.

(Response) FDA notes that the comments did not challenge the accuracy of FDA’s estimate, rather they challenged what FDA recommends in the guidance. FDA believes that the estimate of the burden of the proposed collection of information is accurate.

9. Payment or Gift

This information collection does not provide for payment or gifts to respondents.

10. Confidentiality

This information collection will only be used to aid developers of new non-pesticidal proteins determine the safety of their new protein. Consistent with confidentiality requirements, FDA will make submissions of early food safety evaluations for new proteins, and FDA’s responses thereto, easily accessible to the public via the Internet.

11. Sensitive Questions

This information collection does not involve any questions of a sensitive nature.

12. Burden of Information Collection

FDA estimates the burden for this information collection as follows:

Table 1.--Estimated Reporting Burden¹

	No. Of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
4 easy data elements	20	1	20	4	80
2 original data elements	20	1	20	16	320
Annual one time burden hours					400

¹ There are no capital costs or maintenance costs associated with this information collection.

Burden:

Hour Burden Estimate

One Time Burden

Submitting an early food safety evaluation for a new plant protein will be a one-time burden (one submission per new protein). As this guidance is voluntary, FDA cannot

know how many developers will choose to submit an early food safety evaluation for their plant protein. Many developers of novel plants may choose not to submit an evaluation because the field testing of a plant containing a new protein is conducted in such a way (e.g., on such a small scale, or in such isolated conditions, etc.) that cross-pollination with traditional crops or commingling of plant material is not likely to be an issue. Also, other developers may have previously communicated with FDA about the food safety of a new plant protein, for example, when the same protein was expressed in a different crop.

FDA scientists predict that this guidance will generate about 20 to 150 early food safety evaluations yearly. While there is uncertainty as to the number of evaluations that developers will choose to submit, FDA estimates that the annual number of early food safety evaluations will be closer to the lower bound estimate of 20 evaluations rather than the upper bound estimate of 150 evaluations. This estimation is supported by the fact that on average there have been nine initial biotechnology consultations per year. An initial biotechnology consultation has traditionally been the first discussion between a developer and FDA about a food made from a new bioengineered plant variety; it is usually bioengineered varieties of plants that are the subject of a consultation with FDA.

Evaluation Components

The early food safety evaluation for new proteins from new plant varieties includes six main data components. Four of these data components are easily and quickly obtainable, having to do with the identity and source of the protein. FDA estimates that completing these data elements will take about 4 hours per evaluation. In table 1 of this document, row 1 shows that for 20 evaluations, the total burden for these four data requirements is 80 hours.

Two data components ask for original data to be generated. One data component consists of a bioinformatics analysis which can be performed using publicly available databases. The other data component involves 'wet' lab work to assess the new protein's stability and the resistance of the protein to enzymatic degradation using appropriate in vitro assays (protein digestibility study).

These data components will be completed in the course of study on the new protein whether or not the company submits an early food safety evaluation to FDA. Therefore, the paperwork burden of these two data elements consists only of the time it takes the company to put together the information on these two data elements to submit to FDA. Given that the 4 easy data elements are expected to take 4 hours to prepare per evaluation, it is reasonable to assume that the two more involved data elements will each take twice as long to complete for the early food safety evaluation. Therefore, for each evaluation, these two data components will take 16 hours to complete (8 hours for each component, doubled from the 4 hours it takes to complete the simpler components of the early food safety evaluation). Table 1 row 2 shows that for 20 evaluations, the total burden for these two data requirements is 320 hours.

13. Capital Costs (Maintenance of Capital Costs)

The data components generated for an early food safety evaluation of a new protein will be completed in the course of study on the new protein whether or not the company submits an early food safety evaluation to FDA. Therefore, there are no additional capital costs or operating and maintenance costs associated with this collection.

14. Annual Cost to Federal Government

FDA estimates that the staffing burden for review of early food safety evaluations will be 80 hours per submission. We estimate that we will receive approximately 20 submissions annually. Thus, we estimate 1600 hours will be needed to review early food safety evaluation submissions. The cost to the Federal government is estimated as being equivalent to the number of hours of review per year at an average hourly salary rate of \$48.18, which is the hourly salary rate for a GS-13/Step 10 for the Washington-Baltimore locality pay area for year 2006 (1600 hours x \$48.18/hour = \$77,088). This estimate also presumes that overhead will be equal to salary for a total cost to the Federal government of approximately \$154,176 per year ($\$77,088 \times 2 = 154,176$).

15. Reason for Change

This is a new collection.

16. Statistical Reporting

FDA plans to assign a number to each submission and create a list of the submissions for posting on the Internet. The information on the Internet will include a hyperlink to the text of each submission (other than confidential commercial information) and a hyperlink to FDA's response.

17. Display of OMB Approval Date

There are no reasons why display of the expiration date for OMB approval of the information collection would be inappropriate.

18. Exceptions to "Certification for Paperwork Reduction Act Submissions" of OMB Form 83I

No exceptions to the certification statement identified in Item 19 of the instructions for completing OMB Form 83-I have been identified.