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Comments on Draft Guidance for Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use; Docket No. 2004D-0369

The Center for Food Safety appreciates the opportunity to comment on the draft guidance for early food safety evaluations. The purpose of the proposed guidance is to indicate the types of safety evaluations that FDA recommends the food industry perform while genetically engineered (GE) crops remain under development and are grown outdoors in field trials. The impetus for this guidance is an Office of Science and Technology Policy (OSTP) directive from 2002 directing regulatory agencies to address contamination of food by experimental GE crops.

The likelihood of such contamination has become increasingly apparent after several widely publicized contamination incidents. StarLink Bt corn, not approved for human consumption because of allergenicity concerns, nevertheless contaminated the food supply, leading to an expensive recall and fines. In 2002, several instances of contamination of food crops by biopharmaceuticals in field trials conducted by Prodigene, discovered shortly before entering the food supply, raised concerns that experimental genes with no food history and that had not been evaluated for safety, could enter our food. Although not involving a food crop, the recent report of contamination of wild bentgrass by transgenes

from GE creeping bentgrass up to 13 miles from the field trial site, reinforces the likelihood that contamination of food crops by transgenes will occur.[a]

In fact, we really have no idea how frequently such contamination may be occurring because testing for contamination from field trials has rarely been done. There are, however, close to a thousand field trials of experimental transgenic crops per year in the U.S., regulated by the Department of Agriculture (USDA). These crops contain experimental genes that usually do not undergo any food safety evaluation, which typically does not occur until the food developer wants to commercialize the crop. Commercialization does not occur until after several years of field trials aimed at determining the performance of the crop. In many cases, the genes used in field trials, and the transgenic proteins they produce, are never evaluated for safety because the experimental crops are never commercialized. Of the over 10,000 experimental GE crops that received field trial permits or notifications over the past 18 years, only about 93 have been submitted to FDA for safety review. Therefore, the vast majority of experimental genes that may contaminate our food supply are never evaluated for food safety.

The potential hazards from GE crops have been extensively considered and recognized by a number of scientific bodies, including several committees of the National Academy of Sciences. These hazards include allergenicity or toxicity of the GE protein and allergenicity or toxicity caused by unintended adverse changes in the GE crop. Such adverse consequences can also occur upon consumption of food contaminated by transgenes and their proteins.

For these reasons, it is critical that thorough risk assessments of GE crops are performed prior to field trials when there is a chance of contamination of food. The FDA draft guidance, however, does not demand a thorough risk assessment of all GE crops that may contaminate our food. Instead, the proposed FDA guidance, has a number of weaknesses that perpetuate and exacerbate the problems with the current GE food safety testing regulations at FDA. Unless these failings are remedied, the proposed guidance will serve to institute a system largely incapable of ensuring the safety of GE foods.

The failings of the proposed guidance include:

1) **As with FDA's current regulation of GE foods, the proposal on "early food safety evaluation" is voluntary and not a safety approval process.**

The draft guidance therefore suffers from all of the weaknesses of the current FDA review process. Only a minority of GE food crops are expected to be submitted to FDA for review. FDA estimates that only 20-150 requests for early reviews will be submitted, and most likely closer to 20. However, there are typically close to 1000 new field trials of experimental GE crops per year that may contaminate food. **Therefore, many new genes will not be reviewed for safety.** Compared to the current situation, FDA's guidance will only marginally increase the number of food safety evaluations for experimental transgenic proteins that may contaminate food.

FDA gives no guidance on which GE crops undergoing field trials should undergo safety testing, instead leaving this judgment to the crop developer. Field trials with minimal confinement strategies that may have allowed contamination in the past will therefore continue to go untested.

2) **The proposed guidance would further weaken current safety testing by recommending that only the GE protein be reviewed for safety.**

The focus on the GE protein alone excludes testing for the well-known unintended harmful changes that may occur in genetically engineered plants. These unintended effects are due to unexpected changes in the plant rather than to the direct effects of the transgenic protein, and are included in the full FDA safety review (although not adequately assessed). There are dozens of published examples of such unintended effects, and they were recently the subject of a National Academy of Sciences report, which acknowledged that harmful unintended effects may occur from GE.[b]

FDA provides no adequate explanation of why unintended effects are not evaluated. However, it may be that FDA considers that what it calls low and intermittent exposure to contamination from GE crops makes the assessment of unintended effects unnecessary. However, without a detailed assessment of specific types of unintended effects, and the range of potential toxicity and exposure levels, it is premature to assume that harm would not occur. Some effects may occur at extremely low exposures. For example, food allergenic reactions may occur at parts per billion concentrations for some food allergens, such as peanuts. Allergenic proteins that occur at very low levels might increase to levels that could cause serious reactions. The same may be true for certain toxins that food crops usually produce at low levels.

3) **The guidance continues to allow GE crop developers to decide how to test the safety of the GE protein, rather than FDA setting safety standards.**

The FDA guidance continues to allow GE crop developers to determine how they will perform the two tests recommended in the draft guidance, rather than providing accepted methodology. The two tests are database searches for similarities between the GE protein and allergens or toxins, and determining the digestive stability of the GE protein *in vitro*. FDA does not recommend testing methods despite published research showing that how such tests are conducted determines their accuracy.

For example, research by FDA's own scientists demonstrated that increased concentrations of the digestive protease, pepsin, used in the digestive stability assay, can cause the rapid breakdown of known food allergens.[c d] Rapid digestion is usually associated with non-allergenic food proteins. By using excessively high concentrations of pepsin, some allergens can therefore be made to appear to be non-allergens in this assay. Excessively high concentrations of pepsin have been used by GE companies in the past.[e] So without detailed guidance by FDA on the best way to perform these tests, the possibility for misleading tests and results will continue.

It is especially troubling that FDA does not adopt detailed guidance on allergenicity testing, because an international body convened by the Food and Agriculture Organization and the World Health Organization of the U.N. in 2001 developed testing guidance that has become widely accepted, including by the Codex Alimentarius, the international body that is developing safety standards for GE foods.

4) **FDA is apparently proposing to allow these inadequate safety tests because it assumes that contamination will occur at low levels. However, FDA never sets limits for contamination.**

In some cases, to the contrary, exposure may be quite high. For example, some crops that may be eaten whole could contain substantial amounts of the GE protein (and unintended effects) throughout the food, thereby providing substantial exposure. For example, the endosperm of a seed that develops on a non-GE crop like sweet corn that has been contaminated by pollen from an experimental GE crop, could provide a significant amount of GE protein to someone who consumes it.

5) **FDA does not require any animal feeding tests to determine the potential toxicity of the GE protein or GE food.**

Animal testing is a standard approach to determine toxicity. Many proteins that produce dietary toxicity can be assayed in animals. For example, some lectins and protease inhibitors, components of many plants, including some food crops, will cause adverse reactions in humans and test animals. Although not perfect, animal tests can add some additional confidence to safety testing. Similarly, animal testing of the whole GE food, although not without difficulties, can provide additional useful data on the safety of the GE food.

The FDA guidance provides for only two tests for potential toxicity of the GE protein: a database search for matches with known toxic or allergenic proteins, and a test for gastric stability. The latter test is only an indirect test, which does not determine actual toxicity or lack thereof. Instead, the lack of stability is intended to indicate that the transgenic protein will not survive to enter the intestines, where it could cause harm either directly, of after entering the bloodstream. However, as noted above, changes in test conditions can affect the apparent stability of the protein.

In practice, some proteins show a low or intermediate level of stability, digesting in a few minutes rather than a few seconds for unstable proteins and non-allergens, or one or more hours for many food allergens. On the other hand, some food allergens are stable for only a few minutes.

Interpretation of these intermediate results is problematic. For example, EPA is putting the issue of digestive stability test results and methodology for a Bt protein, Cry34, before a Scientific Advisory Panel to help it determine how to interpret intermediate stability and other data. Such intermediate results will likely occur with additional GE proteins, and are unlikely to be adequately addressed by FDA's current practice of

uncritically allowing GE food developers to draw their own safety conclusions from the tests they perform.

In addition, it is likely that the food matrix of the GE protein and food processing will affect gastric stability, as will gastric insufficiency disorders. These considerations can alter protein gastric stability *in vivo* compared to *in vitro* results using an isolated GE protein.

Similarly, the lack of similarity between toxins and allergens in a database may only indicate a novel mechanism for GE proteins from organisms that have not previously been in foods.

In sum, the two recommended tests provide an extremely thin set of methods that have substantial weaknesses and may therefore not detect potential harm from some GE proteins. More robust methods are needed, including animal testing.

6) **FDA fails to indicate whether submissions of safety test data for field trials will be made public.**

If tests are not disclosed, the lack of transparency will prevent the public from knowing whether adequate tests are being performed. Lack of transparency will not improve public confidence in the safety of GE foods. [FDA indicates that it will make put the "text of the submission" on the internet, but will consider confidentiality requests. It is not clear whether data are included in the definition of "text."]

7) **FDA does not propose to test for contamination from field trials, and therefore will not acquire data on the frequency and levels of contamination. Lack of testing for contamination may also provide a disincentive for GE crop developers to submit early safety testing data.**

FDA does not currently test for contamination by GE field trials, and does not require GE crop developers to submit reagents or DNA sequences that would allow monitoring for contamination of conventional crops. FDA should require the submission of reagents or data that allows testing for contamination.

Without a program of testing for contamination, GE crop developers will have less incentive to comply with FDA recommendations for early testing, because contamination is likely to go undetected. In addition, the current data on contamination from field trials is all but lacking, so the extent of the problem is unknown. The recent examples of contamination of wild bentgrass by herbicide-tolerant creeping bentgrass, as well as the Prodigene contamination incidents, suggest that contamination from field trials may not be uncommon.[f] For both reasons, it is critical for FDA to begin testing for contamination from field trials.

8) **GE crop developers may see the new FDA guidance as reducing their liability from harm caused by contamination of food from experimental GE crops.**

If GE food developers determine that the FDA guidance reduces potential liability from harm caused by contamination, they may relax confinement procedures. This may in turn serve to actually increase the amount of contamination.

Increased contamination may occur because most GE field trials are performed under USDA notification, which does not require GE crop developers to disclose how they will "minimize" contamination. This leaves the methods for confinement largely up the GE developer. Confinement measures, such as allowing adequate spatial separation from conventional food crops or staggering planting to avoid overlap of flowering with food crops, can be an inconvenience. Therefore, some GE crop developers may decide to cut corners if they believe that liability may be reduced by submitting the recommended tests to FDA, and additionally because there is little likelihood that contamination will be detected due to the lack of testing for contamination under this guidance.

Conclusions

The proposed guidance perpetuates many of the inadequacies of the current regulation of GE foods**,** and does little to enhance the safety of the public. Instead of the proposed voluntary and minimal testing process, rigorous methods to prevent contamination, such as the redundant stringent confinement approach outlined by the NAS, should be required for all field trials.[g] In addition, testing of food crops for contamination by experimental GE crops should be routinely performed to determine if and how much contamination is occurring. Such testing will also encourage compliance with sound confinement procedures. Where complete confinement cannot be assured, thorough safety testing should be required, rather than the watered-down process recommended in the draft guidance.

Given the inadequacy of the recommended tests, and especially the small fraction of experimental GE proteins that are expected to be tested, it is unclear what FDA hopes to accomplish by the proposed guidance. Certainly, when the public understands the limitations of this guidance it will only serve to undermine confidence in the regulatory oversight of GE foods.

Sincerely,

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[b] National research Council, 2004,"Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects," National Academies Press, Washington, DC

[c] Fu, T-J (2002) Digestion stability as a criterion for protein allergenicity assessment. Ann. N.Y. Acad. Sci. 964:99-110

[d] Fu, T-J, Abbott, UR, Hatzos, C. (2002) Digestibility of food allergens and nonallergenic proteins in simulated gastric fluid and simulated intestinal fluid – a comparative study. J. Agric. Food Chem. 50:7154-7160

[e] Gurian-Sherman D, (2003) Holes in the Biotech Safety Net, Center for Science in the Public Interest. http://cspinet.org/new/pdf/fda_report_final.pdf

[f] Watrud et al. op cit

[g] National research Council, 2004, "Biological Confinement of genetically Engineered Organisms," National Academies Press, Washington, DC