THE CENTER FOR FOOD SAFETY

Briefing Paper:

A Look at the Unintended Effects of Genetically Engineering Food Plants Re. the National Academy of Sciences Report on Unintended Effects

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The federal agencies primarily responsible for regulating genetically engineered food — the Food and Drug Administration (FDA), Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) — have requested that the National Academy of Sciences study and report on the regulation of unintended effects of genetically engineered crops to help them better determine the safety of these foods for humans and animals.[a] For the purposes of this paper, unintended effects will be defined as changes in the makeup and function of a genetically engineered plant other than those expected from the new gene and its protein. This paper provides important background information on unintended effects, explains and gives examples of risks from unintended effects, and explains the inadequacies of the current human and animal safety regulation of unintended effects in genetically engineered plants.

Unintended effects can include increases in harmful substances such as toxicants, anti-nutrients, and allergens that food crops normally produce in lower quantities. New or previously unidentified substances could also be unintentionally produced. Plants are particularly adept at making such substances, and although thousands have been identified,[1] the biological effects on humans are typically not fully understood. That many of these substances have powerful effects is demonstrated by the many drugs, and even pesticides, that are derived from plant substances. Many of these substances are absent or at low levels in the edible parts of food crops (or are removed by processing) due to millennia of selection and breeding, although their inactive genes may still be present and could be activated by genetic engineering.

We also know that unintended changes due to genetic engineering are common in crops. [2] There are dozens of reports of unintended effects in the scientific literature despite the fact that such effects are typically not recorded because they are not the object of study. It is widely understood that the vast majority of initial transgenic plants are typically rejected due to unintended changes. Some of those changes are due to the genetic engineering process itself and may be removed during further breeding, but many are due to the new gene and cannot be removed. We usually know nothing about the nature of these defective plants because they are discarded by the crop developers. However, the undesirable unintended effects, such as reduced yields, that are easily

[a] The NAS was not asked to report on possible environmental impacts of unintended effects.

identified by genetic engineering companies and are discarded are not synonymous with the typically "invisible" traits that may harm people.

Because of the uncertainties and unpredictable nature of unintended effects, the Center for Food Safety recommends a rigorous approach for testing the safety of genetically engineered foods. The current voluntary regulatory review by FDA does not provide adequate guidance for safety testing and generally allows companies that develop genetically engineered crops to determine how they will test genetically engineered foods for safety. Even widely recognized harmful toxins, anti- nutrients, and allergens have not been consistently tested for in crops reviewed by the FDA. Such lax testing requirements and oversight cannot be relied upon to identify less predictable public health risks and must be substantially improved before there can be confidence in the safety of genetically engineered foods.

Examination of unintended effects in genetically engineered crops shows that:

- Unintended effects in genetically engineered crops are common, and many unintended changes in such crops have been noted in the scientific literature. Yet it is likely that most unintended effects are never reported because they are rarely the object of research.
- Potentially harmful unintended effects have been noted in non-commercial genetically engineered tomatoes, potatoes, and yeast. Genetically engineered tomato plants passed safety review by FDA, but were subsequently found by academic scientists to be capable of accumulating substantially more toxic heavy metals than a conventional variety.
- Due to limited and inadequate safety testing requirements, unintended changes may easily go undetected. In several instances unintended effects have been discovered years after regulatory review.
- Unintended harmful changes have occurred in several traditionally bred crops including potato, celery, and squash. The National Academy of Sciences has previously cited those incidents in conventional crops to support testing for unintended effects in genetically engineered crops.
- Even widely recognized and agreed upon potential unintended effects have not been consistently measured in genetically engineered foods that have passed FDA review
- Unintended changes may also occur in the engineered gene or protein, and are not always easily detected. Detection of changes in the genetically engineered protein is not adequately addressed in current safety testing protocols.
- The mechanisms causing unintended effects in genetically engineered crops and the likelihood that harmful changes will occur have not been widely studied, are not well understood, and cannot be predicted.
- The causes of unintended effects in genetically engineered crops and other types of crop breeding can be similar in some cases, but differ in others; therefore, understanding unintended effects in crops produced by conventional breeding is of limited predictive value for genetically engineered crops.

For all of these reasons, a rigorous approach to testing for harmful changes in genetically engineered crops should be taken. Center for Food Safety makes the following recommendations:

- Legislation requiring FDA to approve the safety of genetically engineered crops, and that requires FDA to develop detailed testing guidelines to assure that the best test methods are used, should be passed by congress;
- Testing should be conducted for changes in the amounts of all toxicants, anti-nutrients, and allergens known to be produced by the crop. Such testing should include those substances typically produced in very low amounts or not typically produced in the edible portion of the crop;
- Animal testing of whole genetically engineered crops should be conducted (not just testing of the purified genetically engineered protein). These tests should follow proper toxicological procedures such as using sufficient animals to allow adequate statistical power, and examining a broad range of sensitive toxicological endpoints. These tests should be at least sub-chronic in duration and also test for developmental effects;
- New methods to identify changes in the crops, such as proteomics and metabolic profiling, need to be validated for use in risk assessment and incorporated into regulatory requirements. Any observed changes in genetically engineered crops need to be identified and assessed for risk.

Background

The National Academy of Sciences/National Research Council has studied the unintended effects that occur in genetically engineered crops at the request of federal agencies, and has issued a report on their findings. Improved ability to detect and understand unintended effects could lead to improved risk assessment of genetically engineered crops.

Unintended effects in food crops due to genetic engineering are a major concern as a potential source of harm. Because such effects are typically also unexpected, they can be difficult to recognize and assess for safety. A previous NAS report reviewed unintended effects and concluded that harmful unintended effects may occur in transgenic crops and that they should be carefully assessed by regulatory agencies.[3] Although the current NAS report examines the state of knowledge regarding unintended effects, we still know far too little about how such effects occur to draw conclusions about either their frequency, or to accurately estimate their potential for significant harm.

Potentially harmful unintended effects have occurred in several non-commercial genetically engineered foods and genetically engineered yeast.[4] In one example, genetically engineered tomato plants were found to accumulate significantly higher levels of dangerous heavy metals than conventional tomato plants.[b] Similar 1-aminocyclopropane-1-carboxylic acid deaminase (ACCase) tomato plants, created to delay ripening, previously passed FDA's food safety review without detecting their ability to accumulate heavy metals.[c,5] It was only six years after delayed ripening ACCase tomatoes passed safety review at FDA in 1994,[6] that academic researchers discovered their ability to accumulate heavy metal.[7] Although these tomatoes have never been commercialized, they could have been even prior to FDA review because there is no

[b] Several different transformations using the ACCase gene and different promoters gave similar results, but varied in the amount of heavy metal accumulated and tissue deposition. In one case the genetically engineered tomato plants accumulated five times as much cadmium as conventional tomato plants. The researchers tested tomato shoots and roots for heavy metal accumulation, so we do not know what the levels would be in tomato fruit. Also, of course, accumulation depends on the presence and amount of the heavy metal in the soil.

[c] The ACCase gene used in the delayed-ripening tomatoes came from a different bacterial species than the ACCase in the heavy-metal-accumulating tomatoes. However, it is unlikely that the bacterial source makes any substantial difference, because a third bacterial ACCase has also been shown to cause the accumulation of heavy metals in bacteria. See G.I. Burd et al. in reference section.

mandatory requirement for FDA approval for genetically engineered foods. It is important to recognize that the tests conducted by academic scientists that detected the potentially harmful effects in both genetically engineered potatoes and yeast, in addition to ACCase tomatoes, would likely not have been conducted under current regulations.

An unintended effect was also reported in a commercialized GE crop, Bt corn, five years after passing U.S. safety review. Bt corn was found to have higher levels of lignin than conventional corn in 2001,[8] resulting in slower decomposition in the field. It is not known whether higher lignin has any detrimental effect on the environment. However, corn stalks and leaves are an important source of cattle fodder, and lignin makes fodder less digestible, so that some have suggested developing low-lignin genetically engineered fodder crops to improve animal feed. Assessing changes in the quality of genetically engineered animal feed is the responsibility of FDA, but Bt corn passed FDA review without detection of increased lignin.

Toxic compounds produced by crops such as potato, celery, and squash have occasionally been increased by traditional breeding.[9] So we know that substances usually found in small amounts in crops can be increased to harmful levels by unintended effects. The National Academy of Sciences has previously cited those incidents in conventional crops to support testing for unintended effects in genetically engineered crops.[10]

Unfortunately, current FDA regulations cannot be relied upon to detect even the simplest kinds of harmful unintended effects. For example, it is widely accepted that known toxicants, anti-nutrients, and allergens should be tested to determine if they have increased to harmful levels.[11] Examination of data for several genetically engineered crops submitted to FDA revealed that several common anti-nutrients and toxicants such as phytate in corn or several alkaloids in tomato were not measured to see whether they were unintentionally increased.[12] Phytate reduces the availability of phosphorous and several nutritionally important minerals. It is responsible for much of the phosphorus pollution of water from livestock feedlots, and may cause mineral deficiencies in people with diets heavily dependant on corn, such as those in some developing countries.[13]

It is also important to recognize that not all of the potentially harmful substances in crops have been identified and we do not fully understand the functions of many substances that have been discovered. Recent examples of a previously unrecognized chemical in corn that has apparent hormonal effects on mammals, and protein in wheat associated with diabetes, demonstrate that we still have a lot to learn about the composition of crops.[14]

Another type of unintended effect is the unexpected modification of transgenic proteins. Genes code for the basic structure of a protein, its amino acid sequence, but different organisms modify that structure in different ways.[15] In addition, the sequence, or basic code, can be unintentionally altered during transformation of the genetically engineered crop,[16] potentially changing the properties of the protein. Plants often modify proteins differently than other organisms such as animals or bacteria that are frequently the source of genes for genetically engineered crops. Those changes, such as the addition of different carbohydrates, may have health consequences such as by affecting the reaction of the protein with the immune system and allergenicity.[17] The tests currently used may not detect some of these changes, and do not identify whether such changes are harmful.

One of the important tasks of the NAS unintended effects committee was to identify mechanisms by which genetic engineering may cause unintended effects in genetically engineered plants and to compare those mechanisms with other forms of breeding, such as breeding between crops and their wild relatives. However, mechanisms by which a protein new to a crop might interact with the plant to cause harmful changes may be fundamentally different than the ways that other types of breeding cause harmful changes. For example, most of the genes introduced into crops by crosses between wild relatives and crops are likely to be alleles, or genetic variants, of genes already possessed by the crops, as opposed to completely novel genes.

By contrast, the introduction of entirely new genes and proteins may cause interactions with the plant that are not predicted by the mechanisms responsible for unexpected effects due to variations in genes found in a crop and its wild relatives. For example, the appearance of a new toxicant alkaloid in potatoes bred with a wild relative may be due to differences in the biochemical pathways of the crop and wild parent.[18] While not easily predictable, such a result is readily understandable based on the interaction of biochemical pathways. On the other hand, cowpea trypsin inhibitor has no apparent connection to alkaloid biochemical pathways, so there is no obvious mechanism to explain why cowpea trypsin inhibitor in genetically engineered potato plants would cause lower alkaloid production.[19] Similarly, there is no clear way to explain why lignin synthesis would be increased by the introduction of a bacterial toxin gene[20] that has nothing to do with lignin biosynthesis.

There have been far too few studies of either the mechanisms of unintended changes caused by genetic engineering, or the frequency of those changes, to conclude that risks from unintended effects are low. Comparisons with changes caused by other forms of breeding cannot be relied upon to give an accurate picture of changes caused by genetic engineering until more is known about the latter. Unintended changes in genetically engineered plants remain unpredictable.[21]

It is important to consider safety regulations in the context of what is known about unintended changes in genetically engineered crops. Discussing some of these implications was another important charge of the committee. The ability to measure risk depends on our ability to identify unintended changes in the crop that may be harmful, and to perform tests or use previous information to assess the potential for harm (e.g. toxicity) and exposure to those substances. There is broad consensus that some of the known harmful compounds in crops should be measured.

But those measurements do not address the more difficult issue of how to assess risks from unknown or unappreciated plant substances or genetically engineered protein modifications. Continuing discovery of new and potentially harmful substances in crops that could be inadvertently increased by genetic engineering tells us that merely testing a few known crop toxicants and anti-nutrients is not adequate to assure public safety. Technology to identify all changes in the genetically engineered crop, such as proteomics or metabolic profiling, are needed and are being developed, but are not yet used in risk assessment.[22]

Another approach that does not rely on knowing all of the constituents in the plant is the use of animal feeding studies, such as are often done with pesticides, food additives, or drugs. Animal feeding studies with the genetically engineered plant are not required in the U.S. and are not performed in most cases. Despite some limitations, such tests and others provide an assessment of unknown unintended effects, and should be required.

For all of the reasons discussed, we should be cautious in our risk assessment of unintended effects. A rigorous approach should be taken in the safety testing of genetically engineered crops, including: 1) safety approval by FDA should be required for genetically engineered crops using detailed testing guidelines developed by independent and FDA scientists to assure that the best methods are used; 2) thorough measurement of the level of all known toxicants, allergens, and anti-nutrients produced by the crops, including those produced only in tissues other than those that are eaten, and comparing to the most closely related conventional varieties of the crop; 3) testing of the whole genetically engineered food, in addition to the purified genetically engineered protein, in animals using tests designed to provide adequate statistical power and conducted for long enough to detect harm (including developmental effects); 4) validation of proteomic and metabolic profiling techniques to detect unintended changes in thegenetically engineered plant, and determination of the safety of any identified changes.

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