Contains Nonbinding Recommendations

Foods Derived from Plants Produced Using Genome Editing: Guidance for Industry

You may submit electronic or written comments regarding this guidance at any time. Submit electronic comments to http://www/regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2019-D-4658 and with the title of the guidance document.

For questions regarding this document contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1200 or the Center for Veterinary Medicine (CVM) at 240-402-7002.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
Center for Veterinary Medicine

February 2024

Table of Contents

Foods Derived from Plants Produced Using Genome Editing: Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration's (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

A purpose of this guidance is to clarify how FDA's policy statement "Statement of Policy: Foods Derived from New Plant Varieties" (NPV policy) (57 FR 22984, May 29, 1992) applies to foods[2] derived from new plant varieties produced using genome editing.[3] The NPV policy provides scientific and regulatory guidance on foods from new plant varieties. The NPV policy lays out broad, risk-based principles for ensuring the safety of foods from new plant varieties. These principles are sufficiently flexible to accommodate foods from new plant varieties developed using a wide range of techniques. This guidance explains that the principles outlined in the NPV policy apply to foods from genome-edited plant varieties. This guidance also reminds developers of new plant varieties (developers) of their obligations under section 403(w) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which was enacted after the issuance of our NPV policy. In addition, this guidance describes two processes through which developers may voluntarily inform FDA of the steps they have taken to ensure the safety of foods from their new genome-edited plant varieties: voluntary premarket consultations and voluntary premarket

[1] This guidance has been prepared by the Office of Food Additive Safety, Division of Science and Technology in the Center for Food Safety and Applied Nutrition and the Office of Surveillance and Compliance, Division of Animal Food Ingredients in the Center for Veterinary Medicine at the U.S. Food and Drug Administration.

[2] For the purpose of this guidance, unless otherwise specified, "food" means human food and animal food.

[3] Genome editing methods are methods that can be used to produce new plant varieties by creating genetic changes at specific sites in the plant genome. Using deoxyribonucleic acid (DNA) sequence information from a plant, plant breeders can make targeted changes to a plant's DNA sequence to alter expression of traits in the plant. These methods include processes using targeted nucleases (clustered regularly interspaced short palindromic repeat (CRISPR) associated nucleases, zinc-finger nucleases, meganucleases, and transcription activator-like effector nucleases (TALENs)) or targeted oligonucleotides (oligonucleotide-directed mutagenesis) intended to modify a plant's DNA sequence by insertion, deletion, or substitution of nucleotides at a specific site in a plant's genome. The process of producing these targeted DNA sequence alterations is often referred to as "genome editing."

meetings. The voluntary process we recommend for a new food is based on the objective characteristics of the new food, especially those related to food safety.[4]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

In the *Federal Register* of May 29, 1992, we issued a policy statement titled, "Statement of Policy: Foods Derived from New Plant Varieties" (NPV policy; 57 FR 22984). The NPV policy clarifies our interpretation of the FD&C Act as it applies to foods derived from new plant varieties. The NPV policy lays out broad risk-based principles for ensuring the safety of foods from new plant varieties and is sufficiently flexible to accommodate foods from plants developed using a wide range of techniques. The NPV policy discusses scientific issues and provides guidance relevant to the safety assessment of foods derived from new plant varieties. Since issuance of the NPV policy, scientists have gained a greater knowledge of plant biology, genomics, and genetics. At the same time, new methods have been developed to modify the deoxyribonucleic acid (DNA) sequences of plants and to characterize such modifications. In addition, new DNA sequencing methods have made it easier to obtain the DNA sequences of plant genomes. Using a plant's DNA sequence information, plant breeders can now make targeted changes to the plant's DNA sequence to alter traits in the plant (see for example, Yin et al., 2017). These newer methods, collectively referred to as genome editing, include the use of nucleases and/or oligonucleotides intended to modify the plant's DNA sequence by insertion, deletion, or substitution of nucleotides at specific locations in a plant's genome. These methods can be used to produce a range of changes from as little as a single base-pair to the introduction of a gene from an exogenous source.

In the *Federal Register* of January 19, 2017, we published a notice titled "Genome Editing in New Plant Varieties Used for Foods," in which we invited public comment to help inform our regulatory approach to foods derived from plants produced using genome editing (82 FR 6564). We asked for data and information in response to questions about the safety of foods from genome-edited plants, such as the ways in which food safety risks associated with foods from genome-edited plants are the same as or different from those associated with other development methods (e.g., hybridization, chemical or radiation mutagenesis, and non-targeted genetic modifications using *in vitro* recombinant-DNA technologies). We also asked for information about how best to engage small businesses that may be considering using genome editing to produce new plant varieties for food use. We received more than 580 comments in response to

[4] While this guidance does not apply to the safety or legal status of plant incorporated protectants (PIPs) themselves, which are regulated by the Environmental Protection Agency (EPA), this guidance does apply to PIP-containing foods. Specifically, this guidance applies to food safety aspects of a PIP-containing food in the event that a food safety concern is not associated with the PIP. For example, this guidance applies to food-safety-related changes in the food that are not due to the presence of the PIP. Consequently, developers producing plants that contain a PIP should consider this guidance as they develop new genome-edited plants intended for food use.

the notice. Given our experience with foods from genetically engineered plants under the NPV policy—including the more than 200 evaluations we have completed through the voluntary premarket consultation program for foods from such plants that we have operated since 1994—and the information in the comments, we have determined that the risk-based principles laid out in the NPV policy are applicable to foods produced from genome-edited plant varieties.

III. Discussion and Recommendations

A. Plant breeding

Plant breeders have a long history of using genetic variability to develop new varieties that produce safe and nutritious foods. Regardless of technique(s) used in plant development, only very rarely have new plant varieties been identified as the source of food safety concerns. Based on a history of new plant varieties producing safe food, FDA has not found it necessary to conduct routine premarket food safety reviews of whole foods derived from new plant varieties produced through traditional breeding practices (57 FR 22984 at 22988).[5]

Plant breeders require genetic variability to create new plant varieties. Traditional plant breeding relies on genetic variation within a species that may arise spontaneously during cultivation or may be introduced through techniques such as hybridization (including wide-crosses), chemical or irradiation mutagenesis, or other methods (e.g., somaclonal variation). These traditional breeding practices have been shown to create new varieties with genomes containing large-scale rearrangements, deletions, insertions, and substitutions. Spontaneous, chemical, or irradiation mutagenesis alters the plant's DNA at random sites in the genome. Changes at specific locations in the DNA cannot be prescribed as part of the breeding process using these methods. As a result, desirable traits occur at low frequencies, and many rounds of selection are needed to separate desired traits from undesired traits. Beginning in the 1980's, plant breeders began using recombinant-DNA technology as a tool to further expand the genetic variability that can be used in developing new plant varieties. Recombinant DNA technology can be used to introduce genetic material (variation) from any source into plant genomes to create new plant varieties. Genome editing techniques are more recent techniques that can be used to produce new plant varieties by creating genetic changes at specific sites in the plant genome. In addition, genome editing techniques may make it easier for plant breeders to introduce desirable traits in plants that are typically propagated vegetatively and those plants whose breeding cycles or number of sets of chromosomes (ploidy) pose logistical challenges (National Academies of Sciences, Engineering, and Medicine, 2016).

Genome editing methods enable modifications directed to specific DNA sequences within the genome. This allows for greater control over where the genetic modification occurs in the plant's genome and provides plant breeders greater precision in the types of genetic modifications they are producing. Genome editing techniques may be used to mediate directed changes to a single base-pair, several base-pairs, an entire gene, or possibly to direct the

[5] While foods from genetically engineered plant varieties have customarily been the subject of a voluntary premarket consultation with FDA before marketing, these plant varieties represent a small portion of all new plant varieties used for food. Food from plant varieties produced using other plant breeding methods have not historically been the subject of voluntary premarket consultations.

introduction of a gene from an exogenous source to a specific site in the genome (Hilscher et al., 2017). Because genome editing techniques allow for greater control over the site of a genetic modification, new plant varieties produced using genome editing can produce foods with characteristics similar to or even identical to foods from traditionally-bred plants; thus, food from these genome-edited varieties may have the same characteristics as foods from traditionally-bred plants that have been safely consumed in the past.

B. Unintended changes

Plant breeding relies on genetic variability to introduce new traits. In some cases, introducing genetic variability may result in unintended changes to the plant's phenotype [6] and/or to the characteristics of the foods derived from the plant. Some scientists may refer to such changes as "unintended effects" or "unexpected effects." Unintended changes can occur with all plant breeding techniques and their occurrence does not necessarily result in a food safety concern (Institute of Medicine and National Research Council, 2004; National Academies of Sciences, Engineering, and Medicine, 2016; Schnell et al., 2015).[7]

Addressing unintended changes from plant breeding is not new. Plant breeders are experienced with unintended characteristics arising during the breeding process and use practices to eliminate from the variety development process individual plants with characteristics that would negatively affect food safety or nutrition. For example, plant breeders are aware of substances produced by certain plants that can cause harm when consumed in food and take concentrations of these substances into account when developing new plant varieties (Institute of Medicine and National Research Council, 2004; Organisation for Economic Co-Operation and Development 1993a).[8] Plant breeders have historically screened new plant varieties for toxins that are typical of the plant group (i.e., species, genus, family) from which a crop was domesticated and have excluded from commercialization plants that have high concentrations of the compounds (National Academies of Sciences, Engineering, and Medicine, 2016; Glenn et al., 2017). Using this screening process, plant breeders have historically generated new plant varieties that produce food that complies with the safety requirements of the FD&C Act. This screening process also is applicable to ensuring the safety of foods from genome-edited plant varieties. FDA expects that developers will incorporate this screening process in their variety development process for genome-edited plants used for food.

Among the plant varieties used to produce food, only very rarely have foods from new plant varieties raised food safety concerns (Rymal et al., 1984; Kirschman and Suber, 1989; Zitnak

[6] The term "phenotype" refers to an organism's physical or observable traits.

[7] It has been reported that traditional breeding techniques such as chemical and radiation mutagenesis and natural variation result in a greater frequency and randomness of mutations compared to those resulting from genome editing tools (see Graham et. al., 2020 and Sturme et. al., 2022).

[8] When developing new varieties, breeders consider naturally occurring substances that may potentially be harmful including, for example, solanine in potatoes, cyanogenic glycosides in cassava, and cucurbitacin in cucurbits (e.g., cucumber and squash). In some instances, routine preparation is necessary and sufficient to produce safe food and the need for such preparation is well-known. For example, cassava is typically prepared by cooking or soaking because of harmful cyanogenic glycosides in the root, and soybean meal used as animal food must be toasted before consumption to inactivate proteinase inhibitors (Organisation for Economic Co-operation and Development, 1993b.; Organisation for Economic Co-Operation and Development, 1993a).

and Johnston, 1970; Hellanäs et al., 1995). As of 2023, we have completed voluntary premarket consultations on food from more than 200 new biotechnology-derived plant varieties intended for commercialization to ensure an unintended characteristic causing a food to be unsafe under the FD&C Act in these varieties is not present (Food and Drug Administration, 2023).[9] Based on available scientific data and information related to the use of genome editing in plants, unintended changes potentially resulting from genome editing are likely to fall within the scope of unintended changes associated with all other plant breeding practices that have historically produced safe food.

The scientific literature regarding genome editing techniques has referred to certain unintended changes as "off-target effects" of genome editing — that is, modifications that occur at genomic locations other than the intended location(s)[10] (see for example Tsai and Joung, 2016). Traditional plant breeding practices routinely introduce non-targeted DNA modifications. While off-target modifications can occur, the relevant question for FDA is whether the safety or nutritional characteristics of the resulting food have been impacted (see 57 FR 22984 at 22984). It is possible that off-target effects have no impact on the safety of food from the new plant variety. Moreover, if off-target modifications result in varieties (and derived foods) that have undesirable characteristics, we anticipate that the premarket selection process routinely performed by plant breeders would identify such plants and eliminate them from further development (57 FR 22984 at 22991 to 23004; Organisation for Economic Co-Operation and Development**,** 1993a; Organisation for Economic Co-Operation and Development, 1993b; Schnell et al., 2015; Glenn et al., 2017; Graham et. al., 2020).

Intended genetic modifications also can result in unintended characteristics in plants. This can arise from pleiotropic[11] effects and from secondary effects of gene insertion or disruption (Joint FAO/WHO Consultation on the Assessment of Biotechnology in Food Production and Processing as Related to Food Safety, 1991). For example, intentionally increasing levels of a metabolite can unintentionally alter levels of other metabolites in related metabolic pathways. When targeted genetic modifications are made through genome editing, such unintended characteristics are largely predictable and, therefore, can be evaluated on a case-by-case basis. Pleiotropy and secondary effects also occur from non-targeted genetic changes arising from traditional plant breeding methods. Historically, the premarket selection process routinely performed by plant breeders has successfully ensured such changes do not negatively impact food safety (57 FR 22984 at 22990; Organisation of Economic Co-Operation and Development, 1993a (see Chapter II); Kaiser et. al., 2020).

Ultimately, developers are responsible for ensuring that plant-derived human and animal foods are safe and comply with all applicable legal and regulatory requirements. We encourage plant breeders to continue adhering to accepted scientific standards of practice and sound agricultural

[9] In our NPV policy, we recommended that developers consult with us about foods from new plant varieties developed using biotechnology. Since we issued the policy in 1992, developers have routinely done so. FDA maintains an inventory of completed Consultations on Food from New Plant Varieties.

[10] "On-target" effects are modifications that occur at the intended genomic location(s) but are not the intended modification(s). The impact on food safety of an on-target effect would be assessed in the same manner as any other modification.

[11] "Pleiotropy" refers to the condition where a single gene may have multiple effects.

practice as described in the NPV policy (57 FR 22984 at 22991 to 23004) as well as any additional practices that have been implemented since we published the NPV policy.

In addition to the standard premarket selection process performed on new plant varieties by plant breeders, we expect that foods from some plants produced using genome editing may have characteristics that warrant additional molecular, chemical, and/or nutritional analyses. Examples of such foods may include those that contain new proteins that raise toxicological or allergenicity questions, produce substances that have not normally occurred in that food, have an increased/decreased level of a substance typically found in that food,[12] and/or have modified nutritional content.

C. Considerations specific to food for animals

There are several considerations that are specific for plants and their products used in food for animals, including those intended for companion animals such as cats and dogs. Unlike a food in the human diet, an animal food derived from a single plant variety may constitute a significant portion of the animal diet. For instance, 50 percent of the diet of many domestic livestock species consists of field corn, while soybean meal may be included at 30 percent of the diet. In addition, animals may be fed the same or a similar type of diet for their entire lives. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet. For example, plant breeders routinely evaluate the lignin content in traditionally-bred new varieties of alfalfa (a plant commonly used as food for livestock) because increased lignin content may decrease the digestibility of food from the variety (Organisation for Economic Co-Operation and Development, 1993b). Thus, nutrient composition and availability in animal food are important safety considerations for animal health.[13]

Further, animals consume plants, plant parts, and plant by-products that humans do not consume. For example, gossypol, a plant toxicant, is concentrated in cottonseed meal during the production of cottonseed oil. Animals consume cottonseed meal, whereas humans primarily consume cottonseed oil, thus necessitating different safety considerations. For plants primarily grown for human food, plant by-products as well as produce and grains that do not meet production

---

[12] Information on substances typically produced in different plants for use in food can be found, for example, in the scientific literature, Organisation for Economic Co-Operation and Development (OECD) Crop Composition documents (Consensus documents: work on the safety of novel foods and feeds - OECD), the National Research Council's (NRC's) Nutrient Requirement series (Nutrient Requirements of Animals | The National Academies Press (nap.edu)), Feedstuffs (www.feedstuffs.com), and the American Oil Chemists' Society (AOCS) Monograph Series on Oilseeds (Academic Press and AOCS Press). There are multiple database sources that also provide information on quantities of substances produced in foods obtained from plants, including the U.S. Departments of Agriculture's (USDA's) FoodData Central (https://data.nal.usda.gov/dataset/fooddata-central) and the Agriculture and Food System Institute's Crop Composition Database (https://www.cropcomposition.org/).

[13] The OECD publishes documents (Consensus documents: work on the safety of novel foods and feeds - OECD) containing data on the range of values for nutrients in non-genetically engineered plants. These documents can be used as references regarding nutrient content of various plant-derived foods. Because OECD documents do not always address the typical uses of plants in animal food, the nutrient requirement series published by the NRC also is helpful in establishing average nutrient composition of non-genetically engineered plant varieties, and also typical inclusion rates of different plants, plant parts, or by-products derived from new plant varieties in livestock, poultry, aquaculture, and pet food diets.

standards for human food often become components of animal food. Because plants and their by-products represent an important food source for animals, it is important to determine if significant concentrations of toxicants or other harmful plant constituents are present in new plant varieties.

An additional consideration for animal food is the effect on human food derived from animals that have consumed the animal food (i.e., meat, milk, and eggs). The safety of these resulting human foods is an important safety consideration in the evaluation of the safety of foods derived from new plant varieties.

As with food for humans, plant breeders have historically considered the animal food uses of their new plant varieties and have typically produced new varieties whose products are safe and lawful for use as animal food.

D. Potential allergenicity of food for humans

In the NPV policy, we expressly raised concerns about the potential that a known food allergen could be transferred from one food source to another (57 FR 22984 at 22987). FDA explained in the NPV policy that if an allergen were moved into a variety of a plant species that never before produced that allergen, the susceptible allergic population would not know to avoid food from that variety, and that labeling of such foods may be needed to inform consumers (57 FR 22984 at 22987). These scenarios continue to be a very serious concern for FDA. To date, developers have not commercialized plant varieties for human consumption in which a known allergen was transferred from one source to another (Nordlee et al., 1996; National Academies of Sciences, Engineering, and Medicine, 2016). In April 2023, we issued a letter to industry reminding developers and manufacturers of new plant varieties who intend to transfer genes for proteins that are food allergens (including allergens from foods identified as major food allergens) into new plant varieties used for food of the food safety risks of doing so and the relevant legal requirements for these products.[14]

When we developed the NPV policy in 1992, we were unaware of any practical method to predict or assess the potential for new proteins in food to induce an allergic response in humans and we requested comments on this issue (57 FR 22984 at 22987). Since 1992, there have been several initiatives regarding the assessment of potential allergenicity of proteins that are new to the food supply. These initiatives resulted in the adoption by the Codex Alimentarius Commission of the "Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003)" (the Codex Plant Guideline; Codex Alimentarius Commission, 2003 with amendments in 2008). The Codex Plant Guideline includes an annex titled the "Assessment of Possible Allergenicity" (the allergenicity annex) that represents a culmination of work to develop harmonized criteria for the assessment of potential allergenicity of new proteins. The annex acknowledges that, while there is no definitive test that can be relied upon to predict human allergic response to a protein new to the food supply, a "weight of evidence" approach can be used to assess the possible allergenicity of a protein new to the food supply.

[14] FDA Issues Letter to Industry on the Food Safety Risks of Transferring Genes for Proteins that are Food Allergens to New Plant Varieties Used for Food (April 13, 2023).

In our 2006 "Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use," we provide recommendations for assessing the potential allergenicity of a new protein and encourage developers to use the allergenicity annex in the Codex Plant Guideline. We continue to find this approach valuable in assessing the potential allergenicity of proteins new to the food supply and encourage developers to use this approach when assessing the potential for new proteins to induce an allergic response in humans.

Due to the potential safety concerns, we strongly recommend that developers consult FDA before: (1) transferring genetic material from an organism known to produce food allergens into a different food source; (2) modifying the genetic material of an organism to produce proteins similar or identical to those from an organism known to produce food allergens; (3) attempting to change the levels of specific allergens in crops producing foods subject to labeling under section 403(w) of the FD&C Act; and (4) adding to food a new protein whose potential allergenicity is not known.

E. Regulatory status of foods from plants produced using genome editing

FDA explained in the NPV policy that the regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective characteristics of the food and the intended use of the food (or its components) (57 FR 22984 at 22984).[15] While modern molecular biology methods can provide detailed information about the genetic changes in a new plant variety, the objective characteristics of the food ultimately are most relevant to food safety, rather than the breeding method by which the plant was produced or the type of genetic modification introduced (single base pair mutations, deletions, insertions, etc.). Consistent with the NPV policy, the regulatory status of foods derived from plant varieties produced using genome editing will, like that of food from other plant varieties, be based on the objective characteristics of the food and the intended use of the food (or its components). Under the NPV policy, foods (such as fruits, vegetables, grains, and their by-products) derived from plant varieties developed by the new methods of genetic modification are regulated within the existing framework of the FD&C Act, FDA's regulations, and current practice, utilizing an approach identical in principle to that applied to foods developed by traditional plant breeding (57 FR 22984 at 22984).

F. Legal authority

FDA regulates the safety of foods derived from new plant varieties, including varieties produced using genome editing techniques, under the applicable food safety provisions of the FD&C Act. We explain in the NPV policy that sections 402(a)(1), 403, and 409 of the FD&C Act are adequate to ensure the safety of new food ingredients and foods derived from new varieties of plants, *regardless of the process by which such foods and ingredients are produced* (emphasis added). We have considered our authority under the FD&C Act as it relates to new methods of modification and have concluded that sections 402(a)(1), 403, and 409 of the FD&C Act

[15] FDA explained in the NPV policy that the method by which food is produced or developed may, in some cases, help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product (57 FR 22984 at 22984).

continue to provide the primary authority to oversee the safety and labeling of foods derived from new plant varieties, including those produced using new methods of modification. We refer readers to section V of the NPV policy where we discuss our legal authority under sections 402(a)(1), 403, and 409 of the FD&C Act.

After we issued the NPV policy, Congress amended the FD&C Act to make it easier for food allergic consumers and their caregivers to identify and avoid foods that contain major food allergens. Section 403(w) of the FD&C Act requires that the label of a human food containing an ingredient that is, or contains protein derived from, a "major food allergen" declare the presence of the allergen in the manner described by the law. Section 201(qq) of the FD&C Act identifies nine foods or food groups as major food allergens. They are milk, eggs, fish (e.g., bass, flounder, cod), Crustacean shellfish (e.g., crab, lobster, shrimp), tree nuts (e.g., almonds, walnuts, pecans), peanuts, wheat, soybeans, and sesame. Developers should consider their obligations under section 403(w) of the FD&C Act.[16]

G. Voluntary premarket consultations and meetings

The FD&C Act places an obligation on those marketing foods to ensure that the products they offer for sale are safe and lawful. When a food contains an unapproved food additive or color additive, developers must obtain premarket approval from FDA for use of the food additive or color additive (see sections 409 and 721 of the FD&C Act). While there is no FDA premarket approval requirement for new plant varieties as a class, historically, developers of biotechnology-derived new plant varieties have nonetheless voluntarily consulted FDA before marketing because this enables FDA to help developers ensure that foods are safe and legal before marketing.

Below, we lay out two processes through which developers may voluntarily inform FDA of the steps they have taken to ensure the safety of foods from their new genome-edited plant varieties. Which voluntary process we recommend is based on the objective characteristics of the new food, especially those related to food safety. As described below, we recommend a voluntary premarket consultation, using our current consultation process, for foods from genome-edited plants that may be more likely to raise food safety questions or regulatory considerations because they have one or more of the characteristics identified in this guidance. For those foods from genome-edited plants that do not have any of these characteristics and, therefore, are less likely to raise food safety questions or regulatory considerations, we recommend a voluntary premarket meeting.

Participation in these programs is not required by law, but these programs can help developers ensure that they are meeting their legal obligation to market only safe and lawful food. Such consultations or meetings also would provide FDA with an awareness of the genome-edited plant products potentially on the market. This awareness would help inform our knowledge about the general safety of these foods and our oversight of food safety for specific foods from these

[16] For more information related to allergens, including the food allergen labeling requirements of the FD&C Act, please see http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/default.htm.

plants. Regardless of whether a developer participates in the consultation or meeting processes, developers have a legal obligation to market only safe and lawful foods.

a. Voluntary premarket consultations

Since 1994, we have operated a voluntary premarket consultation program for foods from new plant varieties. We intend to continue to offer voluntary premarket consultations on foods from new plant varieties, including those from genome-edited plant varieties. As has been our practice for previous consultations on foods from new plant varieties, when conducting consultations on foods from genome-edited plant varieties, we will use a science-based, case-by-case approach to food safety assessment that considers the objective characteristics of the food and its similarity to foods that have been safely consumed. We are not aware of data or information indicating that the general food safety assessment principles used in previous consultations would not be applicable to consultations on foods from new plant varieties developed through genome editing. Additionally, we are not aware of data or information indicating that the use of genome editing in the development of new plant varieties would raise novel safety concerns regarding the resulting foods. As in the past, the data and information needed to establish the identity, safety, and regulatory status of the resulting food product will vary depending on the nature of the changes, if any, to the food itself.

Our voluntary premarket consultation process provides a mechanism that can be used to help developers determine the regulatory status of food from new plant varieties and ensure that any safety concerns have been resolved prior to marketing. In general, we encourage developers to consult with us to help ensure the safety of food from plants produced using modern biotechnology and foster continued public confidence and transparency in the use of such technologies. In addition, the information we obtain during voluntary premarket consultations enables us to speak confidently about the safety of these foods. The information and experience gleaned from voluntary premarket consultations also informs FDA's work in multilateral standard-setting bodies and other international fora where the safety of these foods, and the scientific assessments supporting their safety, are discussed.

Using a series of flow charts with explanatory notes, the NPV policy provides guidance to developers regarding safety questions that should be considered prior to marketing. We advise developers to consider the flowcharts and explanatory notes in the NPV policy statement when determining whether food from a new plant variety—including one produced using genome editing—is likely to raise a safety or other legal question.

In addition, for foods from genome-edited plants, voluntary premarket consultations may be especially useful when genome editing is used to make any of the types of modifications described below. Foods from varieties with such modifications may raise safety questions or regulatory considerations that put the legal status of the food in question—including whether an added substance, such as a newly expressed substance resulting from genome editing, is an unapproved food additive. Thus, we strongly recommend that developers of genome-edited plants with any of the following modifications engage in a voluntary premarket consultation:

1. Modifications to endogenous genes that create significant homology to a known allergen[17] that is relevant to human health or a toxin that is relevant to human or animal health. One example would be editing DNA sequences in a gene in corn such that the protein expressed from the modified gene now encodes a protein that has significant amino acid sequence homology to a known allergen in soybeans.

   Another example would be editing DNA sequences in a gene in peanuts that expresses a non-allergenic protein such that the protein expressed from the modified gene now encodes a protein that has significant amino acid sequence homology to another peanut protein that is a known allergen. In this case, even though people allergic to the known allergen might already know to avoid peanuts, the genome edit might, for example, result in more people having allergic reactions to peanuts.

2. Modifications that cause a non-negligible increase in levels of potentially harmful components, including toxicants, allergens, anti-nutrients, and other components that can exhibit non-nutritive physiological effects on humans or animals (e.g., wheat with increased gluten content, a tomato with increased levels of tomatine, fruits with increased levels of substances that are neurotransmitters or hormones in humans or animals, fruits with significantly increased levels of bio-active phytoconstituents).

   Intended genetic modifications can cause unintended characteristics in plants. Therefore, we recommend developers consider whether intentional changes to crop composition unintentionally increase levels of potentially harmful components. Some examples may include: (1) reducing levels of one allergenic storage protein in a food could unintentionally cause compensatory increases in levels of other allergenic storage proteins; (2) inhibiting production of one toxicant could shunt metabolic flow into a different pathway, resulting in greater production of a different toxicant; and (3) enhancing accumulation of an essential mineral in a food could enhance accumulation of heavy metals also.

3. Modifications that cause a non-negligible change in the nutritional value (level of nutrient and/or bioavailability) of the food.[18]

   Examples of modifications that would cause a non-negligible change in the nutritional value (level of nutrient and/or bioavailability) in food for humans:

   - Modifications that result in the food containing, at a nutritionally meaningful level, a nutrient found at negligible levels in food from its traditional counterpart

[17] When considering whether a modification has resulted in significant homology to a known allergen, FDA recommends applying the amino acid sequence homology criteria in the annex titled "Assessment of Possible Allergenicity" to the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003; the Codex Plant Guideline) or other appropriate criteria.

[18] We strongly suggest that developers contact us if they have questions about whether an intended change to a food would result in a change to the nutritional value of the food that might warrant a voluntary consultation. In some cases, it may be important for us to have specific details about the intended nutritional change and the magnitude of the change for us to assess whether we would recommend a voluntary consultation or a voluntary premarket meeting.

(e.g., wheat containing significantly increased amounts of iron, fruits modified such that they become sources of vitamin D or preformed vitamin A).

- Modifications that result in nutritionally meaningful reductions to the levels of nutrients (e.g., significant reductions in vitamin C content of oranges, significant reductions in vitamin E in sunflower).

- Modifications that result in increases to the levels of nutrients such that a safety concern may be raised (e.g., increases in the selenium content of Brazil nuts, increases in the content of folate in cereal grains).

- Modifications that introduce nutrients to the food that are limited by regulation in similarly used foods (e.g., introducing docosahexaenoic acid (DHA) or eicosapentaenoic acid in canola[19]).

- Modifications intended to change the fatty acid profile of the food (e.g., oilseeds with increased levels of monounsaturated fatty acids or omega-3 fatty acids).

- Modifications expected to affect the bioavailability of nutrients in the food (e.g., increased expression of a protein known to bind certain essential minerals, making them unavailable during digestion and absorption).

For food for animals, in assessing whether a voluntary consultation may be appropriate, developers should consider the following: nutrient levels in the food; the relative sensitivity of individual animal species and stage of life, with respect to nutritional requirements and toxicity; as well as the potential need for diet reformulation. Developers also should consider the anticipated inclusion rate of a plant in an animal's diet because, although a nutrient may only be present at a low level in food from a new plant variety, that food may still be an important source of that nutrient. The examples below involve changes in the nutrient or anti-nutrient content of new plant varieties and the direct impact of such nutrients in diet formulation. However, we note that changes in the nutrient profile of new plant varieties also may indirectly impact other areas of animal nutrition, and the developer also should consider if this raises potential safety concerns.

Examples of modifications that would cause a non-negligible change in the nutritional value (level of nutrient and/or bioavailability) in food for animals:

[19] Paragraphs (a)(3) and (a)(4) of the Generally Recognized as Safe (GRAS) affirmation regulation for menhaden oil (21 CFR 184.1472) establish limits on the use of menhaden oil to avoid total dietary intake of eicosapentaenoic acid or DHA above 3.0 grams/person/day. Paragraph (a)(3) limits maximum use levels of menhaden oil in specific food categories; paragraph (a)(4) restricts use of menhaden oil in combination with any other added oil that is a significant source of eicosapentaenoic acid or DHA.

- Modifications that result in the food containing, at a nutritionally meaningful level, a nutrient found at negligible levels in food from its traditional counterpart (e.g., elevated levels of vitamin D and calcium,[20] elevated methionine levels[21]).

- Modifications that result in nutritionally meaningful reductions to the levels of nutrients (e.g., significant reductions in essential and/or limiting amino acids).

- Modifications that result in increases to the levels of nutrients such that a safety concern may be raised (e.g., introducing or increasing ferroxidase enzymes, which participate in iron metabolism and are also copper-carrying proteins[22]).

- Modifications that introduce nutrients to the food that are limited by regulation in similarly used foods (e.g., introducing DHA and other omega-3 fatty acids such as eicosapentaenoic acid[23]).

- Modifications intended to change the fatty acid profile of the food (e.g., oilseeds with increased levels of monounsaturated fatty acids or omega fatty acids[24]).

- Modifications that can introduce residues to edible tissues, milk, and eggs from animals fed the new plant variety (e.g., the inclusion of omega long-chain fatty acids in the diet of animals may lead to the accumulation of these fatty acids in eggs, milk, and edible tissues of animals).

- Modifications that affect the bioavailability of nutrients in the food (e.g., phytase expression[25]).

---

[20] The calcium and vitamin D requirements for broiler chicken diets are significantly lower than the requirements of these nutrients in layer chicken diets. Thus, modification of vitamin D (or a precursor of vitamin D) or calcium levels in corn, for example, could lead to toxicity in broiler chicken diets, while having minimal effect in layer chicken diets.

[21] Formulated diets for monogastric animals often do not have an ideal amino acid balance without the addition of specific synthetic amino acids, such as methionine (Katz and Baker, 1975). Modification of amino acids profile in corn, soybeans, and wheat could alter the amount of essential amino acids that are added to diets to provide a balanced amino acid profile. However, methionine also can be toxic at high levels.

[22] Sheep are more sensitive to copper levels in the diet when compared to other livestock species. Thus, the developer should discuss the impact of sheep exposure to the new plant variety expressing a mineral-binding protein that accumulates copper in the plant.

[23] Our regulation at 21 CFR 573.615 addresses the use of marine microalgae as a food additive permitted in dry adult maintenance food for dogs as a source of DHA and other omega-3 fatty acids. The regulation, at 21 CFR 573.615(e)(2)(i), limits maximum use level of the food additive to 16.5 pounds per ton of complete, dry, adult maintenance dog food.

[24] Our regulation at 21 CFR 573.492 addresses the use of gamma-linolenic acid safflower oil as a food additive permitted in dry adult maintenance food for dogs and complete dry adult maintenance food for cats as a source of gamma-linolenic acid and other omega-6 fatty acids.

[25] Phytases degrade phytic acid, which leads to increased bioavailability of phosphorus, cationic minerals, and other feed components. If a genome-edited corn variety that expresses high levels of phytase in the grain is used as a substitute for commodity corn, this may alter nutrient digestion in the gut and lead to mineral imbalances or mineral toxicities.

- Modifications that elevate antinutrient levels of animal food (e.g., elevated levels of tannins, such as in sorghum or clover[26]).

- Modifications that disrupt the normal digestive physiology when present at high levels (e.g., elevated levels of lectin in soybeans,[27] modification of fatty acid profile to increase long-chain polyunsaturated fatty acids[28]).

4. Modifications that change how the plant or food from the plant is used, including modifications that:

    - Enable new or different uses in food, including use of plant tissues with no history of safe use in food (e.g., cotton with reduced levels of gossypol in seed such that roasted kernels can be used in food for humans).[29]

    - Render inappropriate certain historical uses of food from the plant (e.g., an oilseed in which the fatty acid composition is modified such that the oil is no longer suitable for frying; or a forage crop with increased lignin content to prevent lodging,[30] but that renders the crop unsuitable for animal food).

    - Alter the manufacturing properties of a food for animals (e.g., modification of resistant starch content in corn would alter the pet food extrusion process and characteristics of the kibble).

    - Alter properties of food in the animal digestive tract (e.g., modification impacting glucanase, which alters viscosity of digesta in digestive tract; modification impacting xylanase, which alters resistant fiber levels in digestive tract).

5. Modifications that introduce: (a) new genes and/or genetic elements that do not naturally occur in that species; or (b) additional copies of endogenous genes that are retained in the genome once genome editing is complete. We would ordinarily consider genes and/or

---

[26] Condensed tannins are a class of secondary plant metabolites that are found in several forage plants and sorghum grain. Condensed tannins possess various antimicrobial, anti-parasitic, anti-oxidant, and anti-inflammatory activities. However, condensed tannins at high levels are considered antinutrients because they can impair the digestion of various nutrients, especially proteins, and can inactivate digestive enzymes such as trypsin and chymotrypsin (Barry, 1989).

[27] The alteration of plant architecture or modification of the expression of a transcription factor in the plant could lead to higher levels of lectin in the plant. This could alter availability of carbohydrates or glycol-conjugates (glycoproteins, glycolipids, and polysaccharides), resulting in an alteration in carbohydrate metabolism, and impact digestive physiology (Popova and Mihaylova, 2019).

[28] The addition of high levels of polyunsaturated long-chain fatty acids to diets for ruminant animals may cause disruption of rumen fermentation (Niwinska et al., 2011).

[29] We recognize that traditional plant breeding has resulted in foods with new uses and that such foods may have historically been safely consumed. In cases where genome editing is used to make the same modifications, a voluntary premarket consultation would not ordinarily be warranted. Examples of such modifications would be those resulting in foods such as sweet corn and waxy maize from varieties not previously associated with these characteristics. Sweet corn (Walker, 2018) and products of waxy maize (e.g., cornstarch) (Schwartz and Whistler, 2009) have been safely used in foods in the United States for decades.

[30] Lodging is when a plant falls over and does not return to a standing position.

genetic elements introduced into the genome through a transformation event and retained in the final product to be examples of these types of modifications.

New genes and/or genetic elements may come from organisms that have not historically been used in the food supply and/or may have chemical functions new to the food supply such that their use in food is more likely to raise questions about whether the expressed protein or new substance would be an unapproved food additive. FDA also recognizes that a possible consequence of transferring genetic material from one source into another is the possibility of introducing a food allergen that would not be expected to be in a particular food. For example, it is possible to transfer genes from one food organism to an unrelated food plant, thereby allowing the potential transfer of an allergen from the first organism to the second. The transfer of an allergen from one food organism to another could raise significant food safety concerns because consumers would not ordinarily expect the new food to contain an allergen from a different food.

We recognize that there may be instances in which new genetic elements are inserted into the genome of a plant that are non-functional and inconsequential to food safety (e.g., components of border sequences used in Agrobacterium-mediated transformation; incomplete and non-functional regulatory components such as promoters, enhancers, or transcriptional terminators). In such cases, a voluntary premarket consultation may not be warranted, and a voluntary premarket meeting may be appropriate. If a product presents such a case, we suggest the developer talk to us about the specific product and whether a consultation would be warranted.

If there are questions about whether a product has any of the above characteristics, we encourage developers to contact us.

b. Voluntary premarket meetings

For those foods from genome-edited plants that do not have any of the characteristics described above, we strongly recommend that developers schedule a voluntary premarket meeting with us to share information about the food and its food safety characteristics. The purpose of a voluntary premarket meeting is to familiarize us with the types of foods from genome-edited plants entering the market and the steps developers have taken to ensure their safety and lawfulness. During these meetings, developers should describe the safety characteristics of human and animal food from their new variety (including whether the food has characteristics that would suggest a voluntary premarket consultation instead of a voluntary premarket meeting) and explain the steps they have taken to ensure that food from their new variety is safe and lawful. We intend to summarize each voluntary premarket meeting in a memorandum of meeting that we will store in our files.

Voluntary premarket meetings are not intended to substitute for a voluntary premarket consultation when foods have characteristics, such as those laid out above, that may raise food safety questions or regulatory considerations not amenable to resolution during a simple meeting. Along the same lines, a voluntary premarket meeting is not intended to represent an FDA evaluation of a developer's food safety assessment similar to the evaluation we conduct as part of a completed voluntary premarket consultation. To inform stakeholders of our activities in this

area, we intend to maintain on our website a list of voluntary premarket meetings. However, if safety and/or regulatory questions arise based on information presented during the developer's narrative, we intend to discuss those with the developer during the meeting or through follow-up communications.

Voluntary premarket meetings are within the spirit of the long-standing practice of voluntary, informal consultations between developers and FDA before marketing food from biotechnology-derived plant varieties. These meetings provide an opportunity for FDA to help developers ensure that foods from genome-edited plants are safe and legal before marketing and, as in the case of voluntary premarket consultations, provide us with an awareness of the genome-edited plant products potentially on the market.

Developers have an obligation under the FD&C Act to ensure that the foods they offer to consumers are safe and comply with all applicable legal requirements. Because, in some cases, a developer may have questions about the regulatory status of a food from a genome-edited plant, developers can informally meet with FDA before marketing a food from genome-edited plants to ensure that the food's safety and regulatory status is properly resolved.

c. Initiating a voluntary premarket consultation or a voluntary premarket meeting with FDA

Developers can begin engaging us in a voluntary premarket consultation or voluntary premarket meeting by contacting us at: plantbiotech@fda.hhs.gov. We encourage developers to meet with us early in their product development process and as often as necessary to resolve any concerns. Early engagement with FDA about food from a specific new plant variety may help identify the data and information most relevant to food safety or other concerns specific to food from the new variety. Developers with limited regulatory experience may find engagement with FDA early in their product development process especially beneficial. Developers interested in participating in the voluntary premarket consultation process may wish to view completed consultations on FDA's website.

H. Early food safety assessment

Separate from premarket consultations or meetings, we recommend that developers consult, when relevant, FDA's 2006 guidance on the early food safety assessment of new[31] non-pesticidal[32] proteins expressed in new plant varieties (see "Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use," June 2006). In the 2000s, we developed an early food safety assessment program, referred to as the New Protein Consultations program (NPC program), whereby developers can consult us in the early stages of development about the potential toxicity and allergenicity of new non-pesticidal proteins intended to be expressed in new plant varieties. The NPC program helps ensure that new, non-pesticidal proteins are not toxins or allergens, and provides guidance about the assessment of potential

[31] In this context, "new" refers to a protein that has not been evaluated through either an early food safety evaluation or a biotechnology consultation, regardless of the plant species into which the protein is introduced.
[32] This 2006 guidance does not apply to PIPs, which are regulated by EPA.

allergenicity for new proteins. While the early food safety evaluation guidance was intended to address food safety concerns associated with the inadvertent low-level presence of new varieties in the food supply, our experience has been that the safety assessment performed during an evaluation in the NPC program may address relevant food safety issues associated with the intended presence of the protein in the food supply as well. We encourage developers producing varieties with new non-pesticidal proteins to continue engaging in the NPC program before material from the variety might inadvertently be present in the food supply, such as during field testing.

I. Regulatory status at other federal agencies

The Coordinated Framework for the Regulation of Biotechnology (51 FR 23302, June 26, 1986), most recently updated in 2017, explains that new plant varieties and products derived from them may be regulated by more than one federal agency based on the nature of the alteration and applicable legal authority. For example, plants and their products may be subject to regulatory oversight by USDA's Animal and Plant Health Inspection Service (APHIS), the Environmental Protection Agency (EPA), as well as FDA. APHIS enforces the Plant Protection Act and regulates organisms that may pose a risk to plant health. EPA's enforcement of the Federal Insecticide, Fungicide, and Rodenticide Act as well as EPA's authority to establish tolerances under section 408 of the FD&C Act, are focused on the safe use of pesticides in the environment as well as the safety of any pesticide chemical residues in or on food.[33] The fact that a plant and the products derived from it comply with applicable laws and regulations enforced by APHIS and/or EPA does not mean that food from the plant will necessarily comply with all applicable food safety laws and regulations enforced by FDA. Moreover, the types of data and information necessary to address plant pest issues considered by APHIS and pesticide safety issues considered by EPA may differ from the data and information necessary to address food safety issues considered by FDA. We encourage developers to engage FDA before marketing when they have questions about whether food from their new plant variety presents any food safety or other legal issues.

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Barry, T.N. "Condensed tannins: Their role in ruminant protein and carbohydrate digestion and possible effects upon the rumen ecosystem." In: Nolan, J.V., Leng, R.A. and Demeyer,

[33] FDA is responsible for enforcing tolerances for pesticide chemical residues in or on domestic foods shipped in interstate commerce and foods offered for import into the U.S., except for meat, poultry, *Siluriformes* fish (including catfish), and certain egg products that are regulated by the U.S. Department of Agriculture.

D.I. *The roles of Protozoa and Fungi in Ruminant Digestion: proceedings of an international seminar held at the University of New England, Armidale, Australia, 26-29th September, 1988*. Penambul Books, Armidale, NSW Australia. pp. 153-169, 1989.

2. Codex Alimentarius Commission. *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003)*, Food and Agriculture Organization of the United Nations: World Health Organization, Rome, 2003 with amendments in 2008.*

3. Food and Drug Administration. "Consultations on Food from New Plant Varieties." Accessed at https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=NewPlantVarietyConsultations December 6, 2023.*

4. Glenn, K. C., Also, B., Bell, E., Goley, M., Jenkinson, J., Liu, B., Martin, C., Parrott, W., Souder, C., Sparks, O., Urquhart, W., Ward, J. M., Vicini, J. L. "Bringing New Plant Varieties to Market: Plant Breeding and Selection Practices Advance Beneficial Characteristics while Minimizing Unintended Changes." *Crop Sciences,* 57:2906, 2017.

5. Graham, N., Patil, G. B., Bubeck, D. M., Dobert, R. C., Glenn, K. C., Gutsche, A. T., Kumar, S., Lindbo, J. A., Maas, L., May, G. D., Vega-Sanchez, M. E., Stupar, R. M., & Morrell, P. L. "Plant Genome Editing and the Relevance of Off-Target Changes." *Plant Physiology*, 183(4): 1453–1471, 2020.

6. Hellanäs, K. E., Branzel, C., Johnsson, H., Slanina, P. "High levels of glycoalkaloids in the established Swedish potato variety Magnum Bonum." *Journal of the Science of Food and Agriculture,* 68: 249-255, 1995.

7. Hilscher, J., Bürstmayr, H., Stoger, E. "Targeted modification of plant genomes for precision crop breeding." *Biotechnology Journal,* 12: 1600173, 2017.

8. Institute of Medicine and National Research Council. 2004. *Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects.* Washington, DC: The National Academies Press. https://doi.org/10.17226/10977.

9. Joint FAO/WHO Consultation on the Assessment of Biotechnology in Food Production and Processing as Related to Food Safety. "Strategies for assessing the safety of foods produced by biotechnology- Report of a Joint FAO/WHO Consultation." World Health Organization, Geneva, 1991.

10. Kaiser, N., Douches, D., Dhingra, A., Glenn, K. C., Herzig, P. R., Stowe, E. C., Swarup, S. "The role of conventional plant breeding in ensuring safe levels of naturally occurring toxins in food crops." *Trends in Food Science & Technology*, 100: 51-66, 2020.

11. Katz, R.S. and Baker, D.H. "Methionine toxicity in the chick: nutritional and metabolic implications." *Journal of Nutrition* 105(9): 1168-75, 1975

12. Kirschman, J. C., Suber, R. L. "Recent Poisonings from Cucurbitacin in Traditionally Bred Squash." *Food and Chemical Toxicology,* 27: 555-556, 1989.

13. National Academies of Sciences, Engineering, and Medicine. 2016. *Genetically Engineered Crops: Experiences and Prospects.* Washington, DC: The National Academies Press.

14. Niwinska, B., Bilik, K., Andrzeuewski, M. "Factors influencing rumenic and vaccenic acid content in cow's milk fat." *Annals of Animal Science*. 11: 3-16, 2011.

15. Nordlee, J. A., Taylor, S. L., Townsend, J. A., Thomas, L. A., Bush, R. K. "Identification of a Brazil-Nut Allergen in Transgenic Soybeans." *The New England Journal of Medicine,* 334: 688-692, 1996.

16. Organisation for Economic Co-Operation and Development. *Safety evaluation of foods derived by modern biotechnology: concepts and principles*. Paris, 1993a.

17. Organisation for Economic Co-Operation and Development. *Traditional crop breeding practices: an historical review to serve as a baseline for assessing the role of modern biotechnology*. Paris, 1993b.

18. Popova, A. Mihaylova, D. "Antinutrients in plant-based foods: A review." *The Open Biotechnology Journal*, 13: 68-76, 2019.

19. Rymal, K. S., Chambliss, O. L., Bond, M. D., Smith, D. A. "Squash Containing Toxic Cucurbitacin Compounds Occurring in California and Alabama." *Journal of Food Protection,* 47: 270-271, 1984.

20. Schnell, J., Steele, M., Bean, J., Neuspiel, M., Girard, C., Dormann, N., Pearson, C., Savoie, A., Bourbonnière, L. Macdonald, P. "A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments." *Transgenic Research*, 24: 1–17, 2015.

21. Schwartz, D. and Whistler, R. L. "History and Future of Starch." *Starch: Chemistry and Technology, Third Edition.* Elsevier, Inc., 2009.

22. Sturme, M. H. J., van der Berg, J. P., Bouwman, L. M. S., De Schrijver, A., de Maagd, R. A., Kleter, G. A., Battaglia-de Wilde, E. "Occurrence and Nature of Off-Target Modifications by CRISPR-Cas Genome Editing in Plants." *ACS Agricultural Science & Technology,* 2 (2): 192-201, 2022.

23. Tsai, S. Q., Joung, J. K. "Defining and improving the genomewide specificities of CRISPR–Cas9 nucleases." *Nature Reviews Genetics*, 17: 300-312, 2016.

24. Walker, S. "Home and Market Garden Sweet Corn Production-Guide H-223." Cooperative Extension Service, College of Agricultural, Consumer and Environmental Sciences, New

Mexico State University, 2018 (available online at: https://pubs.nmsu.edu/_h/H223.pdf; accessed June 16, 2023).

25. Yin, K., Gao C, Qiu J. L. "Progress and prospects in plant genome editing." *Nature Plants,* 3: 17107, 2017.

26. Zitnak A., Johnston, G. R. "Glycoalkaloid content of B5141-6 potatoes." *American Potato Journal*, 47: 256-260, 1970.