



Gene-edited organisms in agriculture:

Risks and unexpected consequences

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Logos Environmental

About Logos Environmental

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Gene editing creates GMOs; it entails humans directly altering genetic material.

Executive Summary



Gene-edited crops that have bypassed USDA oversight include: white button mushrooms, wheat, soybeans and waxy corn.

In the U.S., companies are racing to incorporate genetically modified organisms (GMOs) produced using new genetic engineering technologies such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and other “gene editing” (or “genome-editing”) techniques into our food system with little to no oversight and public disclosure, despite scientific research that is demonstrating the potential for significant unintended consequences.

For example, in a recent study published in *Nature Biotechnology*, scientists from the Wellcome Sanger Institute in the UK found that new genetic engineering techniques like CRISPR may cause “genetic havoc”. Specifically, researchers found large deletions and rearrangements of DNA² near the target site that were not intended by researchers.³ Prior to that study, two recent independent studies published in *Nature Medicine*, one by the biotech company, Novartis and the other by the Karolinska Institute, found that cells genetically engineered with CRISPR “have the potential to seed tumors”,⁴ or may initiate tumorigenic mutations.⁵

Earlier studies found that gene-edited plants such as soybeans had off-target effects, in which gene editing occurred at unintended locations with DNA sequences similar to the targeted location.⁶ These studies are a small sample of the growing research demonstrating the unintended consequences and surprise impacts that may result from genetically engineering organisms.

The new genetic engineering techniques are being proposed for a wide range of applications from pharmaceuticals to genetic therapy in humans to agriculture.⁷ Within agricultural proposals, the most common trait for gene-edited plants is herbicide tolerance.⁸ This prevalence implies that, like current genetically engineered crops, the application of techniques like CRISPR will further entrench a chemical-intensive approach to agriculture. In fact, the first product to go to market was Cibus’ SU Canola™, which is resistant to the herbicide sulfonylurea.

The unexpected and unintended effects of all genetically engineered organisms, regardless of whether ‘traditional’ or gene-edited genetic engineering techniques have been used, have the potential to cause environmental and human

health problems.⁹ While some studies describe gene editing such as CRISPR as “precise,”¹⁰ most studies have been “proof of concept” studies that look at specific intended changes that might be achieved. But these studies haven’t looked at collateral effects of gene editing, such as unintended changes to DNA in other genes. As the current research shows, precise edits do not necessarily result in precise outcomes. Additional concerns about gene editing applications in agriculture include increased agrochemical use, effects on pollinators, impacts from stacking genetically engineered traits and genetic contamination of crops’ wild relatives.

While recent studies raise concerns about unintended effects, more research is needed to understand the implications of CRISPR and other engineering techniques on non-target genes and surrounding ecosystems. Yet food products such as the CRISPR mushroom¹¹ are being allowed into fields and onto the market in the U.S., with insufficient evidence to demonstrate their safety,¹² without regulatory oversight and without being labeled as GMO products.

In this report, we highlight the unintended effects and potential risks related to gene editing applications in agriculture as reported in peer-reviewed scientific studies. We emphasize significant research and data gaps in the analysis of how the unintended genetic mutations resulting from gene editing may impact human health and ecosystems. The report provides recommendations for further research and points to the lack of regulatory oversight in the U.S. We also address the question of whether gene editing in agriculture is necessary, as modern conventional breeding offers an alternative, and possibly better, option in the development of new varieties of plants and animals.

What is gene editing?

Gene editing is a set of new genetic engineering techniques for altering the genetic material of plants, animals and microbes, such as bacteria, using “molecular scissors” that are aimed at a location on the organism’s DNA and used to cut

the DNA. This cut DNA is then repaired by the cell’s own repair mechanism.

These techniques result in GMOs. Any artificial manipulation that invades living cells for the purpose of altering its genome¹³ in a direct way, including gene editing, constitutes genetic engineering.

CRISPR

One of the most popular and recent types of gene editing technologies is CRISPR. CRISPR cuts DNA at a specific location using molecular scissors known as site-directed nuclease (SDN). It then inserts, deletes or otherwise alters a specific gene. Although CRISPR has been touted for its potential to be a precise genetic engineering tool, recent studies caution that using CRISPR can have unintended effects on DNA and gene regulation and could create serious problems, like potentially interacting with a cancer prevention gene in human cells¹⁴.

Gene drives

Gene drives, using CRISPR, are proposed to engineer the genetics of entire populations^{15,16} by forcing a specific trait through generations of a species and bypassing the process of natural selection. Once released, gene drive organisms cannot be recalled, and any changes to the genetic makeup of the population they induce are most likely irreversible. Hence, the genetic changes to a population are likely to persist for a very long time, possibly permanently. This may result in far-reaching and unpredictable consequences for society and the environment.

Proposed uses of gene drives are still in the “proof of concept” stage. They include genetically engineering mosquitoes to prevent effective reproduction, thus reducing the mosquito population as a vector of diseases,¹⁷ or altering the genes of agricultural pests to suppress their populations¹⁸. While such applications appear to promise societal benefits, concerns surrounding gene drives are severe. Given the magnitude of risk, 170 civil society organizations from around the globe are urging



Gene-edited traits could be stacked with other GMO traits, potentially affecting toxicity to wildlife.

a moratorium on gene drive development.¹⁹ Scientists have likewise cautioned that gene drives could foster far-reaching, harmful impacts if any unintended effects were to occur.²⁰

The need for regulatory oversight of gene-edited plants and animals in agriculture

Initial scientific assessments of CRISPR and other new genetic engineering techniques and the high potential for unintended consequences demonstrate the importance of a robust governance structure and a precautionary approach to gene editing.²¹ Yet, the current regulatory structure in the U.S. is a patchwork of weak oversight split between the U.S. Environmental Protection Agency (EPA), U.S. Department of Agriculture (USDA) and U.S. Food and Drug Administration (FDA). As a result, some of the most common types of gene editing technologies, such as CRISPR, can avoid essential regulation and assessment in the U.S. The EPA requires virtually no assessment of the environmental impact of gene-edited organisms, while the USDA only regulates gene-edited plants if they involve plant pests or are themselves plant pests.²² The FDA has no mandatory requirement for food safety assessment and technically has authority to

assess gene-edited animals, but the standards for doing so are unclear.²³ Once they are on the market in the U.S., gene-edited products may not be identifiable to consumers or retailers, as the current proposed GMO labeling regulation under debate in the U.S. may not cover gene-edited organisms.²⁴

Given the prevalence of unintended consequences from genetic engineering applications, all genetic engineering techniques should fall within the scope of government regulatory oversight of genetic engineering and GMOs. In July 2018, the European Court of Justice set an important precedent by ruling that second wave genetic engineering techniques, like ODM (oligonucleotide-directed mutagenesis) and CRISPR, will be included within the European regulations developed for first-wave genetic engineering technologies.²⁵

The United Nations Convention on Biological Diversity (CBD) is also leading important international dialogue about the governance of second-wave genetic engineering. The CBD is currently deliberating global recommendations for precautionary guidelines to govern genetic engineering with particular attention to gene drives.

Conclusion

Research and regulations are not keeping pace with developments in genetic engineering. New genetic engineering techniques, like CRISPR, require further analysis in the context of agricultural ecosystems and the food system as a whole in order to properly assess their potential risks and hypothetical benefits. Along with science-based assessments of health and environmental risks to address significant gaps in scientific knowledge, the scope of analysis should be expanded to include social, cultural and ethical considerations as well as extensive public discussion to determine the future of gene editing in agriculture. More robust research and regulations on gene editing are needed across the international community, with special attention given to potential impacts on human and environmental health alongside inclusive public discourse on the topic.

Alternatives to gene editing are proving to be less risky and highly effective.²⁶ Assisted by a growing understanding of DNA and genomes, techniques like genomic selection²⁷ and marker-assisted selection can now speed up the selection of desirable traits in conventional breeding. Such approaches have already achieved success in producing disease-resistant crops²⁸ and improving cattle, pig and chicken breeding.²⁹ Innovative conventional breeding options such as these should be explored further as a viable solution to developing a precautionary, safe, equitable, sustainable and just food system.

Key Findings

- Gene-edited organisms are prone to unintended and unexpected effects at the molecular level that may pose a threat to human health and the environment if commercialized without comprehensive mandatory safety assessment and oversight.
- Gene drives, designed to drive a particular trait through the entire population of a species, could have far-reaching and unpredictable negative consequences for organisms and the environment.
- The prevalence of herbicide-tolerant gene-edited plant proposals³⁰ implies that gene editing applications will further entrench a chemical-intensive approach to agriculture.
- In the U.S., current regulations may allow gene-edited organisms into the environment and onto the market without assessments or labeling.
- There are gaps in research about how unintended consequences at the genetic level may impact the whole organism or interact with complex environmental factors. More robust research is needed, particularly about potential impacts on human and environmental health.

Recommendations for international and national regulators

- Any deliberate, artificial manipulation that invades living cells for the purpose of altering its genome in a directed way, including gene editing, constitutes genetic engineering. All genetic engineering techniques should fall within the scope of government regulatory oversight of genetic engineering and GMOs.
- The products of all techniques of genetic engineering, including gene editing, should be regulated using the Precautionary Principle to protect human health and the environment.
- Oversight and regulations should include independent assessment for safety and other long-term impacts before entering the market or environment, and products of all genetic engineering should be labeled and traceable.



Gene editing can produce large deletions and complex rearrangements of the organism's own DNA.

Overview

“These CRISPR-modified crops don’t count as GMOs.”³¹ “This gene editing tech might be too dangerous to unleash.”³² Headlines about new genetic engineering techniques have spread across the globe. The genetic engineering techniques may be new, but GMOs and their associated environmental impacts, such as the increased use of glyphosate-based Roundup herbicide,³³ have been of concern for the past 20 years. Now, genetic engineering is being trumpeted under a different guise, using names such as gene editing or genome editing. Despite the publicity of its potential applications in agriculture,³⁴ gene editing is raising concerns.

Gene editing is genetic engineering, as it involves using laboratory techniques to alter DNA.³⁵ Although promoted on the basis of largely unsubstantiated claims of specificity and precision, gene editing techniques — like all types of genetic engineering — can cause unexpected and unpredictable effects. Despite this, gene-edited plants are bypassing USDA oversight,³⁶ meaning there is no environmental safety assessment of these genetically engineered crops, even though they could have far-reaching consequences.

This report discusses the concerns with gene editing as documented by published scientific studies, highlights the gaps in scientific assessments and points to the need for regulatory oversight requiring health and environmental safety assessments of gene-edited organisms. Many scientific studies have now highlighted specific genetic errors that can be created by gene editing — including so called “off-target” effects. However, studies have not yet been conducted on what the implications of these errors might be for food and environmental safety. The scope of published studies also shows a gap in broad public dialogue about the use of gene-edited plants and animals in agriculture and about how they are assessed, labeled and employed (if at all) in agriculture. For any gene-edited organism, it is vital that detailed studies are performed prior to any outdoor growing or entry into

the food chain. These studies should evaluate any potential negative impacts on human and animal health, the environment and biodiversity and should all be taken into consideration by regulators in accordance with the Precautionary Principle.³⁷

Issues with gene-edited organisms

Technical

- Gene-edited organisms are a new type of genetic engineering, leading to the creation of GMOs.
- Gene editing is prone to generating genetic errors, leading to unexpected effects in the resulting GMO.
- Food and environmental safety could be affected by the unexpected effects caused by gene editing.

Societal values

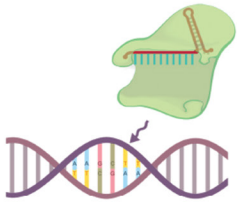
- The regulatory system lacks consideration of societal values.
- Gene-edited organisms in food may not be labeled as GMOs.
- Gene-edited organisms are not essential for agriculture — advanced conventional breeding is delivering new varieties.



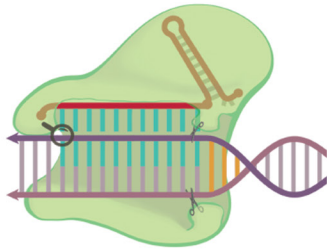
Regulatory

- Gene-edited organisms require careful assessment of any genetic errors and unexpected effects.
- Loopholes in the U.S. regulatory system allow GMOs to evade risk assessment.
- Gene-edited organisms undergo risk assessment in many other countries and regions of the world, e.g. EU.

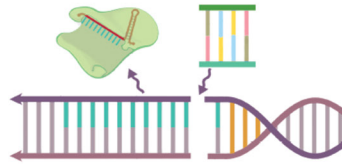
How gene editing works



“Molecular scissors” (nucleases) are guided to a location (the target site) on an organism’s DNA.



The molecular scissor complex docks onto the target site and cuts through the DNA.



The repair of DNA is then initiated and occurs either with (SDN2) or without (SDN1) a synthetic repair template. Alternatively, genes can be inserted (SDN3).



The DNA is now “edited.” However, in reality, gene editing is prone to creating unintended changes and errors that can lead to unexpected effects in the gene-edited organism.

Defining genetic engineering

Current genetically engineered crops, e.g., Roundup Ready soy and Bt corn, have been made using “standard” genetic engineering. Standard genetic engineering — as devised in the 1970s — inserts genes (made up of DNA) at a random location into an organism’s own DNA, or genome.³⁸ If those genes are from a different organism (often called “foreign” genes), then the resulting GMO is transgenic. Almost all current commercial genetically engineered crops are transgenic, with the inserted gene(s) normally producing a protein that makes the plant tolerant to a particular herbicide (e.g., Roundup Ready soy), or toxic to certain plant pests (e.g., Bt corn).

Genetic engineering is very different from conventional breeding. Conventional breeding has been used by farmers and breeders for thousands of years³⁹ to develop plant and animal varieties with desired traits, such as grain or milk with superior qualities or resistance to pests and diseases. In plants and animals, conventional breeding relies on normal male and female mating to produce offspring with desired traits that are then selected for further breeding. In contrast, genetic engineering does not rely on mating to obtain desired traits. Instead,

researchers directly alter the genetic material of an organism using laboratory techniques. It is this direct alteration of genetic material by humans that defines genetic engineering in the U.S.⁴⁰ and underpins the definition of a GMO in the United Nations⁴¹ and the European Union⁴².

Genetic engineering does not rely on mating to obtain desired traits. Instead, humans directly alter the genetic material of an organism by using laboratory techniques.

What is gene editing?

Gene editing (also called genome editing) is a set of new genetic engineering techniques for altering the genetic material of plants, animals and microbes, such as bacteria. All such techniques use a synthetic molecular guide with the goal of changing DNA while it is present in the organism, i.e., in situ. The change in the organism’s genetic material is achieved not through the breeding process (as in conventional breeding), but directly and artificially by humans using the same, or similar, laboratory techniques as genetic engineering. This means that gene editing, like genetic engineering, produces GMOs.

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The most talked-about gene editing technique is CRISPR⁴³, but there are several gene editing techniques that all follow the same basic principles. Molecular scissors are aimed at a location on the organism's DNA and cut the DNA. This cut DNA is then repaired by the cell's own repair mechanism. The type of repair is the key to how gene-edited organisms are classified. Depending on how the repair is achieved (see Box, right), there are three different types of gene editing: one that uses a synthetic repair template, one that doesn't use a synthetic repair template and one where a gene (or genes) are inserted.⁴⁴

The principal difference between "standard" genetic engineering and gene editing is that genes do not necessarily have to be inserted into the organism to produce a new trait,⁴⁵ although the molecular scissors must be introduced into the organism. The resulting gene-edited organism may or may not produce a novel protein as part of the novel trait, as most current commercialized GMOs do. However, even if a gene-edited organism does not contain foreign genes or express a novel protein it cannot be considered "safe" for the environment or food on this basis alone. In addition, the developer may, or may not, have introduced foreign DNA and may or may not know if it is still there (see Intended and unintended insertion of DNA). As explained in Unexpected Effects below, the process of gene editing, like standard genetic engineering, can give rise to unexpected and unpredictable effects in the resulting GMO.

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Different types of gene editing

Gene editing techniques such as CRISPR, TALEN, ZFN and meganucleases⁴⁶ guide molecular scissors (known as site-directed nucleases, SDNs) to the location on the genome where the DNA change is intended to take place. Depending on the technique, these guided molecular scissors are in the form of synthetic proteins, or synthetic RNA-protein combinations. The molecular scissors cut the DNA, which then undergoes repair using the cell's own repair mechanism. Often, a synthetic DNA template is used to direct the repair in such a way that a particular change in the DNA is achieved.⁴⁷ This gives rise to different types of gene editing:

- 1) No repair template is used (SDN type 1 or SDN1)
- 2) A repair template is used (SDN type 2 or SDN2)
- 3) Genes are inserted during the gene editing process, usually giving the resulting organism a particular trait. This gene editing results in a transgenic organism if the genes are from other species. (SDN type 3 or SDN3).

The most common type of molecular scissors used with CRISPR is called "Cas9," so people often refer to the CRISPR-Cas9 system, but other types of molecular scissors are also possible, e.g., Cpf1.⁴⁸ In addition, a new CRISPR strategy is under development called base editing. Base editing uses molecular scissors that don't cut all the way through the DNA, but unravel the DNA, allowing a small (single base pair) change to the DNA to take place.⁴⁹ However, the concerns regarding genetic errors created during the gene editing process still apply to base editing.

The gene editing technique known as oligonucleotide-directed mutagenesis (ODM) does not use guided molecular scissors, but instead introduces a short strand of DNA that attaches itself to the organism's DNA at a particular location and causes a change to that DNA.⁵⁰



Although often described as “precise,” genetic engineering, including gene editing, is prone to creating genetic errors.

Gene editing applications under development

Gene editing is being proposed for a wide range of potential traits. Pilot or “proof of concept” studies demonstrating feasibility for both plants and animals have been published in scientific journals. On animals, they include the development of pigs with resistance to certain diseases⁵¹ and “double-musled” beef cattle, which raise ethical concerns because the over-developed muscles can cause breathing problems⁵² and other health issues. There is also research on gene-edited insects for use in gene drives (see [Gene Drives](#)). For plants, gene-edited traits under development include drought tolerance in corn, virus resistance in cucumbers, altered flowering time in tomatoes and altered composition in soybean.⁵³ However, the most common trait for plants is herbicide tolerance.⁵⁴ This suggests that, like current genetically engineered crops, the primary interest in gene editing is developing herbicide-tolerant crops. In fact, one of the first gene-edited products to be commercialized in North America was an herbicide-tolerant canola.⁵⁵

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Unexpected effects with gene editing

Although gene editing techniques are often described as “precise”⁵⁶ compared to standard genetic engineering, these techniques can cause unintended alterations to genetic material (as described below), just like standard genetic engineering. Indeed, the same claim of accuracy and specificity was the basis of standard genetic engineering techniques now known to induce errors (see [Intended and unintended insertion of DNA](#)).⁵⁷ Such unintended alterations or genetic errors can give rise to unexpected effects. Furthermore, even when the intended alteration occurs, unexpected effects can occur because gene-edited organisms may behave differently in the natural environment than expected from laboratory experiments. Tissue culture may also be involved in the gene-edited process, as it often is with standard genetic engineering techniques, which can also result in unexpected changes (mutations to DNA) effects.⁵⁸ While there are many “proof of concept” studies demonstrating what intended changes gene editing might achieve, there is a complete lack of studies on what the implications of any unexpected effects arising from the gene editing process and/or the engineered trait could be for food and environmental safety.

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Most studies on the potential uses of gene editing techniques in agriculture consider off-target effects to be both a major challenge and a major concern.

Unexpected “off-target” effects

One of the main ways gene editing can be imprecise and create genetic errors is by causing “off-target” effects — changes to other genes that were not intended. Off-target effects could unintentionally alter important genes, causing changes in chemistry or protein production — both of which are important for food and environmental safety. Most studies on the potential uses of gene editing techniques in agriculture consider off-target effects to be both a major challenge and a major concern,⁵⁹ and as detailed below, many studies have now detected off-target effects in gene-edited plants and animals.

Off-target effects are caused by the gene editing process occurring at additional unintended location(s) with similar DNA sequences to the intended (target) location. This gene editing causes an unintended change to the DNA at an unintended (off-target) location.⁶⁰ The frequency of off-target effects depends on the gene editing technique and the exact protocol used,⁶¹ but the CRISPR-Cas9 system appears to be particularly prone to off-target effects.⁶² Such off-target effects have been detected in many studies on gene-edited plants, e.g., rice, soybean⁶³ and wheat⁶⁴.

Off-target effects are also a concern in gene-edited farm animals, such as pigs and cattle,⁶⁵ and have been detected in gene-edited mice⁶⁶ and human cells⁶⁷. However, some studies report a lack of detectable off-target effects in gene-edited animals.⁶⁸ This could be because, although the off-target effects may be present, it is difficult to distinguish between off-target effects and natural genetic variation.⁶⁹ In order to evaluate any potential risks posed by any gene-edited plant or animal that is grown in the environment and/or is intended for food, it is important that any off-target effects are fully

evaluated to determine if they have caused any changes to chemistry or protein production.

Unexpected “on-target” effects

In addition to off-target effects, gene editing can also cause “on-target” effects, where the intended change occurs at the intended location, but has a different outcome than expected. A small insertion or deletion of DNA within a gene, even if on-target, could change the way a gene is read and processed into proteins in problematic ways. Essentially, genes in DNA are “read” to produce an intermediary product (RNA⁷⁰), which is then processed into proteins. Studies have found that CRISPR can inadvertently cause extensive deletions and complex re-arrangements of DNA.⁷¹ These deletions and re-arrangements of DNA by CRISPR may cause important parts of the gene (those coding for protein production) to be “missed” when the DNA is read.⁷² This misreading of DNA has the potential to produce altered proteins. Food allergens are mostly proteins, so altered proteins could have significant implications for food safety.⁷³ Concerns with the allergenicity of proteins have long been an important concern with GMOs created by standard genetic engineering techniques. For example, genetically engineered Starlink corn was only approved for animal, not human, consumption in the U.S. because of concerns over the potential allergenicity of the inserted insect resistant gene (Bt Cry9C). After it was found contaminating human food supplies, it was withdrawn from the market.⁷⁴

The misreading of DNA in a gene-edited plant or animal could impact biodiversity. For example, if the chemistry of a gene-edited plant or animal were changed by the misreading of DNA, it could produce a compound that is toxic to the wildlife that feeds on it. These types of concerns regarding human and ecological safety mean that gene-edited organisms need to be analyzed for any on-target effects, and the implications of on-target effects need to be carefully evaluated.

Gene edits to DNA may unintentionally affect the operation of the organism's regulatory network. This could result in the organism's own (unedited) genes not being expressed as they should be, perhaps expressed in the wrong amount, the wrong composition or at the wrong time.

Interference with gene regulation

In addition to altering an organism's DNA, gene editing may have unintended impacts on an organism's ability to express or suppress other genes. Within an organism, genes are switched on (expressed) and off in different parts of the organism at different times as the organism grows, reproduces or responds to environmental factors such as light, heat or drought. In addition, genes interact with each other, either suppressing or reinforcing their expression. The orchestration of gene function in an organism is part of a complex regulatory network. However, the precise way that this regulatory network operates is complex and still poorly understood, as exemplified by recent advances in our knowledge of how gene expression is regulated.⁷⁵ For example, for several decades, a dominant theory in molecular biology was that each gene had a single function (i.e., produces one protein), but it is now known that genes can have several functions and interact with each other.⁷⁶ Similarly, DNA that did not produce proteins was thought to be "junk" DNA, but it is now thought that much of this junk DNA is important for controlling gene expression in plants, animals⁷⁷ and human genomes⁷⁸.

There have already been reports of an unexpected response from the cell regulatory network during gene editing. In experiments with human cells, the cuts in DNA created by CRISPR were unexpectedly found to kill cells or stop them from growing.⁷⁹ The lack of understanding about how genomes are regulated means it is not possible to predict the nature and consequences of all the interactions between altered genetic material (whether intentionally or unintentionally altered) and other (unedited)

genes within the organism. This means that gene edits to DNA may unintentionally affect the operation of the organism's regulatory network. This could result in the organism's own (unedited) genes not being expressed as they should be, perhaps by being expressed in the wrong amount, the wrong composition or at the wrong time.

As these examples show, scientists' understanding of genetics and how genes are regulated is still highly provisional. Gene editing may even be "precise," but the outcomes are not always precise. Just like all genetically engineered organisms, gene-edited organisms may exhibit unexpected and unpredictable effects as a result of unforeseen interactions between the altered genetic material, the organism's own (unedited) genes and its regulatory network. Any unexpected and unpredictable effects could result in alterations to biochemical pathways or protein composition that could have implications for food and environmental safety.

Gene editing may even be "precise," but the outcomes are not always precise.

Intended and unintended insertion of DNA

Many variations of gene editing are in development. However, most of the gene-edited plants developed so far have used a similar process to conventional GMOs. During a typical CRISPR gene editing process, a DNA "cassette" (a suite of genes) containing the CRISPR components is inserted into the organism's genome at a random location — in the exact same way that standard GMOs are created. The inserted cassette produces the CRISPR-Cas9 complex of protein and RNA that performs the genetic change. Afterwards, the inserted CRISPR DNA cassette may then be bred out via conventional breeding so the organism is no longer transgenic (i.e., it no longer contains genes from another species). The gene-edited high fiber wheat produced by Calyxt, a biotech startup, was developed in this way.⁸⁰ However, it is inevitable that not all the inserted DNA will



The most common trait for gene-edited plants is herbicide tolerance.

always be removed. Despite this, no procedures, safety-related or otherwise, are in place to evaluate with this eventuality.⁸¹

In some gene-edited plants, the CRISPR DNA cassette is introduced into the organism's cell and performs the gene editing without becoming integrated with the organism's own genome, as is claimed with DuPont's gene-edited waxy corn.⁸² However, the introduced DNA could unintentionally become integrated, at random, into the organism's genome.⁸³

When DNA is inserted into an organism's genome, the insertion may not be precise. Whether the DNA is intentionally or unintentionally inserted, multiple copies and additional fragments of the DNA cassette can be introduced into the organism's genome.⁸⁴ The insertion of DNA can also cause sections of the organism's own DNA to become rearranged, as has often happened with standard genetically

engineered crops.⁸⁵ Even though the inserted DNA may be subsequently removed through conventional breeding, it is especially possible that fragments could remain undetected and rearrangements of the organism's own DNA could persist. Additional fragments and rearrangements of DNA could give rise to unexpected effects in gene-edited organisms, creating the same concerns as current GMOs. For example, the gene editing could have implications for food and environmental safety if it alters the chemistry (and therefore the toxicity) or the protein composition (and therefore allergenicity) of the organism.

Potential effects of gene-edited organisms on biodiversity and the environment

There are many "proof of concept" publications about what gene editing might achieve, but none of the potential products from gene editing have been examined for what their engineered trait (or any unexpected effects) might mean for the environment and biodiversity. There are large gaps in the scientific knowledge. As with standard genetically engineered crops, there are many concerns regarding negative impacts on biodiversity, including the effects of genetically engineered crops on butterflies⁸⁶ and increased use of herbicides such as glyphosate.⁸⁷ Unfortunately, many warnings about standard GMOs' negative impacts on the environment and biodiversity have been ignored. For example, warnings from scientists about the inevitable rise of glyphosate (the active ingredient in Roundup) tolerant weeds and diminishing biodiversity in agricultural fields⁸⁸ associated with the use of Roundup Ready genetically engineered crops⁸⁹ went unheeded by regulators. The warnings that genetically engineered crops could not be controlled have played out with ongoing contamination of food from genetically engineered crops worldwide.⁹⁰ Such warnings must not go unheeded with gene-edited organisms.

It's important that any potential impacts on biodiversity from the engineered trait(s) in gene-edited crops are evaluated prior to being grown

outdoors. For example, how might changes such as flowering time impact pollinators that rely on flower nectar for food? Such effects are important as many crop species are essential for agricultural biodiversity and pollinators are important for agriculture.⁹¹ In addition, many crops have wild relatives, and these traits could contaminate those wild relatives.⁹² If the trait was to produce a toxic compound, e.g., as an insecticide, this could impact biodiversity if the trait became prevalent in the wild. What might be the impacts of using gene editing in combination with standard genetic engineering in plant crops? Scientists do not yet fully understand the effects of stacking several genetically engineered traits (e.g. tolerance to multiple herbicides and/or multiple types of insect resistance) into a single variety, including how the combinations affect toxicity to wildlife and how all the new genes resulting from genetic engineering interact with one another.⁹³

Small changes — big effects?

The changes to genetic material induced by some types of gene editing techniques (types SDN1 and SDN2) are sometimes described as “mutations”⁹⁴ because only very small parts of DNA (one or a few base pairs) are altered. However, small changes can have big effects. For example, in humans, the disorder known as sickle cell anemia is caused by a single change (a point mutation to a single base pair) in the person’s DNA.⁹⁵ Although mutations do occur naturally, and indeed are an important source of genetic variability in breeding plants and animals, it doesn’t follow that a gene-edited organism with only a small change to the organism’s DNA is always “safe”. To evaluate environmental and food safety, the changes to DNA (both intended and unintended) would have to be carefully evaluated.

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Gene editing (types SDN1 and SDN2, with no foreign genes inserted) could result in greater changes to the genome than just one or a few base pairs if it were to be applied repeatedly, targeted at several genes at once or if the various techniques were used in combination.⁹⁶ For gene editing type SDN3, with genes inserted, it is conceivable that not only could several functional genes be inserted at once, but the changes could result in extensive changes to the genome, so it becomes almost unrecognizable compared to the original organism. Such extensive changes would fall within the scope of “synthetic biology”⁹⁷ and have, so far, been achieved for simple organisms, such as bacteria and yeast.⁹⁸ Therefore, even small edits produced by gene editing techniques can be significant and could potentially result in big changes.

Gene drives

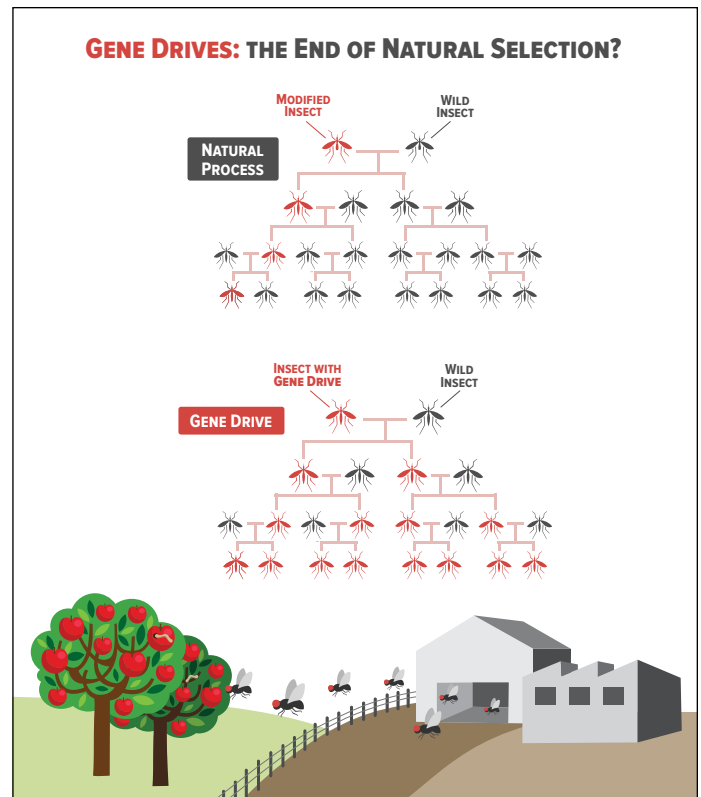
Gene editing techniques, particularly CRISPR (SDN3) systems, have facilitated the possibility of “genes drives.” With gene drive systems, a few gene-edited individuals are used to spread new genes through the entire population of a species.⁹⁹ The gene drive mechanism ensures that the specified new genes will be inherited by every single offspring (as opposed to an expected half of the offspring in normal inheritance) in each subsequent generation.¹⁰⁰ Examples of proposed gene drive systems include altering genes to prevent mosquitoes from reproducing effectively, reducing the size of mosquito populations,¹⁰¹ and a reduction in the susceptibility of mosquitoes to becoming infected with the malarial parasite¹⁰². In agriculture, potential gene drive applications include altering genes so that agricultural pests such as a type of fruit fly (spotted wing drosophila)¹⁰³ and pigweed (Palmer amaranth)¹⁰⁴ don’t reproduce effectively, suppressing their population numbers. Such potential gene drives are currently at the “proof of concept” stage, but there is a concerted research effort into this field.¹⁰⁵

Once released, gene drive organisms cannot be recalled and any changes to the genetic

make-up of the population they induce are most likely irreversible. Hence, the genetic changes to a population are likely to persist for a very long time, possibly permanently. Alongside concerns about who defines what is and is not an agricultural “pest,”¹⁰⁶ scientists are already warning¹⁰⁷ that the consequences of gene drives could be severe should any unexpected effects (for example, those arising from the off-target effects of gene editing¹⁰⁸) or unintended consequences arise.¹⁰⁹

The National Academy of Sciences¹¹⁰ warns that: *“Gene drives developed for agricultural purposes could also have adverse effects on human wellbeing. Transfer of a suppression drive to a non-target wild species could have both adverse environmental outcomes and harmful effects on vegetable crops ... for example, Palmer amaranth is a damaging weed in the United States, but a related Amaranthus species, with which Palmer amaranth can interbreed, is cultivated for food in Mexico, South America, India, China, and Africa. The escape of a suppression drive in Palmer amaranth could affect non-targeted species and negatively impact valued Amaranthus vegetable crops. There are currently no national regulatory mechanisms worldwide that adequately address field testing and environmental releases of gene-drive modified organisms.”*

Gene drives have raised significant concerns among scientists and there have been calls for an international moratorium on gene drive research.¹¹¹ Although only currently at the “proof of concept” stage, concerns are so high among scientists, there is widespread agreement that even research into gene drive systems requires some form of international regulation.¹¹² The United Nations Convention on Biodiversity is considering how to address the issue of gene drives and their possible adverse environmental impacts.¹¹³ However, it is not yet clear whether gene drives for either insects (e.g., mosquitoes) or agricultural plant pests will be regulated at all within the U.S.¹¹⁴



Gene drive organisms cannot be recalled as they are designed to irreversibly change the make-up of a population, giving scientists cause for alarm.

The need for regulatory oversight of gene-edited plants and animals in agriculture

Currently, there is international debate about how gene-edited plants and animals in agriculture should be regulated.¹¹⁵ Gene editing in agriculture is new. It has only recently become commercially feasible, with the CRISPR technique dating from approximately 2012¹¹⁶ and only a few commercialized products, currently limited to plants. Many other countries and regions are in the process of revising GMO regulations to account for gene-edited organisms. Gene-edited plants with genes from another species inserted (type SDN3 gene editing) into them are generally regarded as GMOs by regulatory authorities around the world, as they are very similar to transgenic organisms.¹¹⁷ However, there is deliberation in several countries about whether gene-edited organisms which are not transgenic but which have “edited” DNA (type SDN1 and SDN2 gene editing) should be regulated in the same way as GMOs produced from standard genetic

engineering techniques. For example, in the EU, the European Court of Justice ruled that all gene-edited organisms (including those developed by ODM, SDN1 and SDN2) will be included within the European GMO regulations.¹¹⁸ Australia undertook a public consultation during late 2017/early 2018¹¹⁹ and appears likely to regulate gene-edited organisms developed using SDN2 as GMOs, but the situation regarding SDN1 is unclear¹²⁰. In Argentina, regulators are employing a case-by-case regulation dependent on whether there is a novel combination of genetic material.¹²¹ For Canada, all organisms with “novel traits” are regulated under novel food guidelines which require assessment of all novel food products, whether produced by conventional breeding or genetic engineering, including gene editing.¹²²

In the U.S., the USDA has decided that for genetically engineered plants, it *“does not regulate or have any plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests.”*¹²³ Gene-edited crops may not be classified as plant pests, nor developed from plant pests, and it is usually unclear whether they could have been developed by standard (conventional) breeding. In this way, gene-edited crops are evading regulatory oversight in the U.S.

Normally in the U.S., the developer of a genetically engineered organism would be required to submit a detailed application for the organism to become deregulated (i.e., cultivated without any further notification). However, since 2011, it is estimated that more than 30 transgenic organisms, mostly plants,¹²⁴ and at least six gene-edited plants (see below) have been able to bypass USDA oversight. The USDA arbitrarily regards these organisms as not requiring regulation because they do not involve genes from known plant pests or are not themselves known problematic plants.¹²⁵ Gene-edited crops that have bypassed USDA oversight¹²⁶ include: soybean with drought and salt tolerance, camelina (false flax, similar to canola) with

increased oil content, green bristlegrass with delayed flowering time, waxy corn with altered starch composition, white button mushroom with anti-browning properties¹²⁷ and high fiber wheat.¹²⁸ Although these crops may or may not undergo a voluntary food safety assessment by the FDA,¹²⁹ their status of being non-regulated means that they can be grown outdoors in the open environment without any environmental safety assessment.

The lack of an environmental safety assessment for gene-edited plants raises the possibility that any unexpected and unintended effects present could cause adverse effects on the environment and biodiversity. Such unexpected or unintended effects might go unnoticed by the developers of the product. For example, researchers in the UK using standard genetic engineering techniques to produce genetically engineered plants with omega-3 oils suddenly became concerned after it was found the omega-3 oils unexpectedly produced toxic effects on caterpillar larvae, deforming wings in the adult butterfly.¹³⁰ Such an unexpected but potentially significant effect would almost certainly go unnoticed if there was no requirement to perform any kind of environmental safety assessment on gene-edited crops. The exemption of gene editing techniques in environmental safety assessments could have far-reaching negative consequences. For example, growing gene-edited plants outdoors allows them to cross-pollinate with neighboring crops or their wild relatives, facilitating the spread of their altered genes.

Many scientists are alarmed that gene-edited plants are unregulated in the U.S. As one scientific journal discussed: *“The approach to oversight of GM crops at the US Department of Agriculture shows how a regulatory system can stray from science. GM crop regulations at that agency depend on its authority to control*

The exemption of gene editing techniques in environmental safety assessments could have far-reaching negative consequences.

Gene-edited organisms that do not contain foreign genes or express a novel protein cannot be considered “safe” for the environment or food; unintended effects arising from the gene editing process and any new trait must be carefully considered.

plant pests and noxious weeds. It is a system that had some relevance to the first generation of such crops, many of which were designed using genetic elements from plant pathogens. It is rapidly losing relevance in the face of NBTs [New Breeding Technologies]. In more than two dozen cases, the agency has determined that a particular NBT plant variety does not fall under its purview for regulation because it does not entail the use of a plant pest and is unlikely to yield a noxious weed. These might have been scientifically sound decisions, but they were not made for scientifically sound reasons.”¹³¹

It is not clear whether gene-edited animals would be examined for any potential environmental impacts in the U.S. because there are no specific references to genetically engineered animals in the EPA regulations. However, they would be assessed for food safety under the FDA.¹³²

Since its inception, U.S. regulatory oversight for GMOs has been repeatedly criticized for failing to robustly assess the risks of GMOs.¹³³ Robust regulatory oversight is essential to ensure that the risks of gene-edited organisms are considered prior to them entering the environment or the food chain. Detailed analyses of any unintended effects, inserted genes and new trait(s) in gene-edited organisms are required. Gene-edited organisms that do not contain foreign genes or express a novel protein cannot be considered “safe” for the environment or food; unintended effects arising from the gene editing process and any new trait must be carefully considered.

One of the primary concerns for the food safety of GMOs, including gene-edited organisms, is whether there is any unintended alteration to

protein composition. This is because allergens are proteins, so any inadvertent changes in protein composition could cause the gene-edited plant or animal to trigger allergies in humans (or animals) when eaten.¹³⁴ In the assessment of gene-edited organisms, all hazards need to be identified, no matter how theoretical they might initially appear. Otherwise, there is a danger that potentially damaging impacts could be overlooked. For example, concerns regarding the negative impacts of genetically engineered Bt crops on biodiversity were only articulated a few years after Bt corn had been commercialized¹³⁵ and it was later observed that unexpected changes in the chemistry of genetically engineered Bt corn increased the attractiveness of the Bt corn to aphid pests.¹³⁶

Regulatory oversight is essential to ensure that potential risks of gene-edited organisms are considered prior to them entering the environment or food chain.



Gene-edited organisms require careful examination for unintended effects if they are to be used in agriculture.

In order to avoid any negative impacts on food and environmental safety from gene-edited organisms, there is a need for comprehensive scientific examination of all the potential risks prior to environmental release or entry into the food chain.

Proposals for the regulation of gene-edited organisms in agriculture range from ensuring that they are regulated as genetically engineered organisms¹³⁷ to, at the very least, examining products from gene editing to see if they contain any DNA sequences from the gene editing process¹³⁸. In order to avoid any negative impacts on food and environmental safety from gene-edited organisms, there is a need for comprehensive scientific examination of all the potential risks prior to environmental release or entry into the food chain. These scientific findings should inform regulatory and oversight requirements. In particular, the Precautionary Principle needs to be applied, meaning that full scientific certainty of a possible harm is not needed before preventative action is taken.

In the U.S., it is still unclear whether gene-edited food will be labeled. In the proposed U.S. labeling regulations¹³⁹ for food made from genetically engineered ingredients, the term “bioengineering” refers to genetic material with inserted genes and could exclude a gene-edited food ingredient if the genetic material was “edited” without genes being inserted. Although the proposal is seeking feedback on whether or not to include food produced by gene editing, there is a risk that gene-edited food will go unlabeled as bioengineered, genetically engineered or GMO, disempowering the consumers seeking non-genetically engineered foods. The issue of labeling is also important because the international body for organic agriculture excludes genetically engineered (including gene-edited) organisms from organic systems.¹⁴⁰ Without labeling, it will be impossible to know whether food is gene-edited or conventionally bred.

Regulation and governance are more than science

This report largely focuses on the scientific aspects of gene editing in agriculture, such as the risks and potential consequences to food safety and biodiversity. However, the use (or non-use) of gene-edited organisms in agriculture also depends on societal values. There is a growing awareness that a science-based risk assessment for gene-edited organisms is limited in scope.¹⁴¹ Proposals to expand the scope of the regulations and governance of GMOs beyond scientific concerns include: recognition of the underlying values and assumptions shaping science and innovation, respect for ethical, societal and cultural values, ensuring the sustainability of agricultural systems and the consideration of a range of alternatives to genetically engineered food.¹⁴² One study offers that expanding the scope of governance necessitates the involvement of a broad range of people from different societal sectors to manage the complexity of issues, forming what has been termed a “cooperative governance network.”¹⁴³

There are alternatives to gene editing in the development of new varieties of plants and animals. Conventional breeding has progressed greatly in the past decade,¹⁴⁴ aided by knowledge of DNA and genomes but using this knowledge to assist, rather than replace, conventional breeding. Techniques such as genomic selection and marker-assisted selection allow the selection of desirable traits in plant or animal offspring from conventional breeding based on DNA analysis, greatly speeding up the development of new varieties.¹⁴⁵ These approaches have already produced disease-resistant crops,¹⁴⁶ flood tolerant rice¹⁴⁷ and crops with increased yield¹⁴⁸. These same approaches are also used in cattle, pig and chicken breeding¹⁴⁹. It is key to address the question of whether gene editing in agriculture is necessary to begin with.

Conclusion and recommendations

Gene editing encompasses a suite of new genetic engineering techniques that are being applied to living organisms intended to be used in agriculture. Robust scientific studies document that gene-edited organisms, like standard GMOs, are prone to unexpected and unpredictable effects arising from genetic errors including: off-target effects, on-target effects, interference with genetic regulations and both the intended and unintended insertion of DNA. The engineered trait may also show unexpected interactions with the environment. Applications like gene drives pose particular risks as there can be no recall of such gene-edited organisms and the genetic changes they drive through a population are intended to be permanent.

Despite the significant body of scientific literature demonstrating unintended consequences from gene editing, gene-edited plants are evading regulatory oversight in the U.S. and may already be cultivated in the environment without any safety assurances. There is a risk that food derived from gene-edited crops and animals may go unlabeled, disempowering consumers seeking non-genetically engineered foods and subjecting them to risks such as allergens.

Given the scientific findings of potential unintended consequences from gene editing and the lack of studies concerning health and ecological impacts, government regulatory oversight of all genetic engineering techniques should follow the Precautionary Principle. The products of all genetic engineering techniques (both standard and gene-edited) should be independently assessed for food and environmental safety and other impacts prior to being released into the environment or marketed. They should also be traceable and labeled as GMOs.

While it is critical for more scientific studies to be conducted about the specific impacts of the unintended consequences of gene editing on agricultural systems, ecological systems, human

and animal health, the discussion regarding the use of gene editing in agriculture also needs to go further than a science-based risk assessment to encompass wide public discussion about the future of agriculture.

Suggestions for further reading

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