Gene-edited organisms in agriculture:

Risks and unexpected consequences

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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"[1]. Specifically, researchers found large deletions and rearrangements of DNA[2] 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 mushroom[11] 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 genome[13] in a direct way, including gene editing, constitutes genetic engineering.

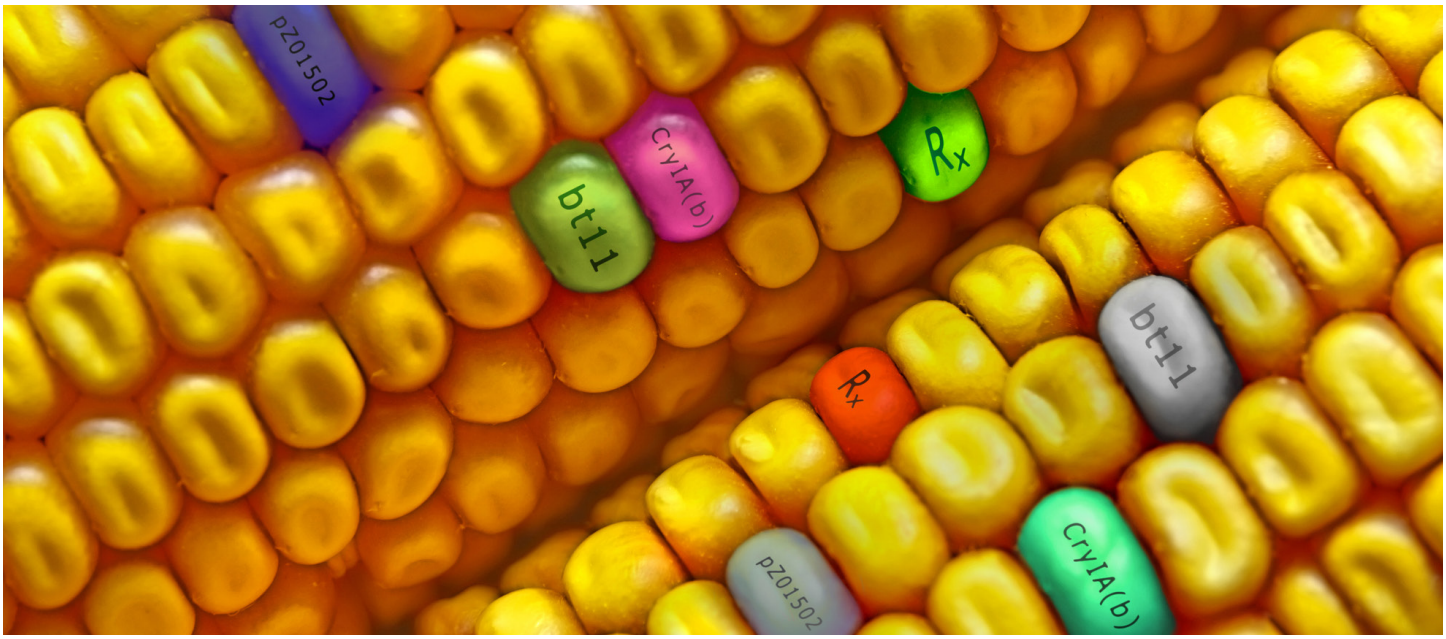
CRISPR

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 cells[14].

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 populations[18]. 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 oversights 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 selection[27] 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 crops[28] 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 proposals[30] 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.

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