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Original article

Genetic Use Restriction Technology (GURT): A paradox of the good evil

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Abstract

Genetic Use Restriction Technology (GURT), also known as "terminator technology", is a type of genetic engineering that renders seeds sterile (V-GURT) or alters a specific trait of a plant (T-GURT), preventing farmers from saving and replanting harvested seeds. GURT can also be of immense benefit to agriculture. It can be used to modify crops for improved traits, such as resistance to pests, herbicides or environmental stresses, which can ultimately improve yields, reduce the need for pesticides and herbicides, and help crops adapt to changing climatic conditions. Despite its potential benefits, GURT technology is restricted in many countries due to ethical and environmental concerns. The debate on the legalisation of GURTs is based on the main issues of food security, biological and environmental impacts, and possible monopolisation of the seed industry by a few large companies. Therefore, in this review we discuss the novelty of GURT technology in crop improvement and the contentious issues that continue to be debated by scientists, policy makers and the public.

Keywords barnase gene, GURT, seed industries, suicide gene, terminator technology

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Introduction

Genetic Use Restriction Technology (GURT) is a two-pronged genetic engineering approach designed to either prevent successful reproduction in certain crop varieties (V-GURT) or to alter/manipulate a specific trait of interest such as pest resistance, germination, flowering, ripening, etc. in a plant (T-GURT) [1-3]. Initially, GURT was a mechanism that allowed the production of viable seeds that could be grown to produce a seed crop, but these seeds would not be viable. It was also known as V-GURT, which refers to variety, or as anti-GM activists call it, 'terminator' technology. This technology uses genetic modification to create plants that produce sterile seeds, making it impossible for farmers to save and replant seeds from their harvests [4, 5]. Around the same time, a second version was proposed in which the seeds produced by farmers were viable, but the engineered enhancement traits were switched off (T-GURT, or Trait GURT or 'traitor' technology). These technologies were designed to protect patented GM technologies and prevent farmers from saving their seeds or other companies from obtaining functional seeds. GURT. This technology was developed by agricultural biotechnology companies in the late 1990s to protect their intellectual property and to prevent farmers from saving and replanting seeds from GM crops, which would reduce market demand for new seeds and their profits, and thus improve breeders' return on investment [6]. Varietal use restriction technologies have been controversial since their inception, with concerns about their potential impacts on food security, farmers' autonomy and livelihoods, and biodiversity [5].

In the 1990s, when the first genetically modified varieties began to appear. Both "terminator" and "traitor" were chosen to convey a negative image of the companies supporting this research. This criticism (deserved or not) was enough to persuade some countries to ban their use, including the Convention on Biological Diversity, effectively ending any potential for their commercialisation. Meanwhile, proponents of terminator technology argue that it is a necessary tool to protect intellectual property rights and to ensure that farmers continue to have access to new and improved crop varieties [7]. GURT also has the potential to improve crop yields, reduce pesticide use or adapt to climate change [2]. It is also thought to help prevent genetic contamination of non-GM crops, which could have unintended environmental consequences, and to encourage the development of new crop varieties. On the other hand, it has been suggested that the technology could negatively affect food security by preventing farmers from saving and replanting their seeds, which has been a widespread practice for millennia, thus limiting farmers' access to quality seed inputs that can adapt to changing environmental conditions [3]. In addition, the use of terminator technology has been criticised for its potential impact on the rights of farmers and indigenous communities, forcing smallholder farmers to rely on patented seeds to grow crops, and creating dependency on corporate-controlled seed supplies [4]. However, it is not clear whether crops developed using T-GURT or V-GURT have ever been commercialised anywhere, and there are no reports of farmers being denied the opportunity to save their seeds as a result of these technologies.

Because of the controversy surrounding terminator technology, it is not yet widely accepted, and some countries have banned its use in crop production. However, as the GURTs encourages research because of the patent rights it gives breeders and its potential to stop the flow of genes [2], it can be seen as good technology, making terminator technology a paradox of good and evil. Meanwhile, the United States has allowed research into terminator technology to continue. Nevertheless, the debate over the technology is likely to continue as scientists and policymakers weigh its potential benefits and risks [3, 8].

Types of Genetic Use Restriction Technology (GURT)

There are two main types of Genetic Use Restriction Technology: Variety Genetic Use Restriction Technology (V-GURT), also known as terminator technology, and Trait Genetic Use Restriction Technology (T-GURT), also known as traitor technology. The Canadian-based NGO Rural Advancement Foundation International (RAFI; now Action Group on Erosion, Technology and Concentration, ETC) was the first to give these two types of GURT their nicknames: terminator-VGURT and traitor-TGURT [9]. In 1990, anti-GM activists also called the product of this technology 'terminator seeds' [10], a kind of fear-mongering nickname. The technology produces first-generation (F_1) seeds, which are sold by the seed company to farmers as fully developed, normal and non-sterile seeds that can produce healthy and improved plants, but the seeds are not viable and therefore will not germinate if planted after harvest. Thus, second-generation (F_2) seeds are not suitable for planting, and farmers have to buy fresh seeds every year because they cannot use the previous year's harvested seeds in the next season [5].

Variety Genetic Use Restriction Technology (V-GURT)

Variety Genetic Use Restriction Technology (V-GURT) involves the genetic modification of plant DNA to produce non-viable seeds at harvest, meaning that harvested seeds will not germinate when replanted [9]. V-GURT was developed in the early 1990s by the Delta and Pine Land Company in collaboration with the United States Department of Agriculture (USDA) [11, 12]. The technology was designed to render F_1 seeds nonviable, preventing farmers from saving and replanting patented seeds. The V-GURT technology works by inserting a terminator gene into the plant's DNA, which produces a protein called ribosome-inactivating protein (RIP), which is toxic to the plant's reproductive cells [3], rendering the seeds non-viable [8]. The gene responsible for the RIP protein can be switched on or off by applying an external chemical, typically tetracycline, which disables the repressor. Seed companies have used this method to begin the process of developing GM seeds before selling them to farmers. This has earned the technology the nickname 'terminator' because it allows the company to control the germination of the seeds [13]. However, in a real sense, neither of these technologies prevents the development of the embryo, which would prevent the production of seeds, the purpose of growing the crop. In the case of V-GURT, the ribosome-inactivating protein is produced only after the embryo and seed have developed, killing the seed once it has matured. In addition, the T-GURT method does not produce sterile or non-viable seeds, only seeds that no longer have the specific trait that has been knocked out. The cavalier use of sterile and suicidal seeds to describe the product of these technologies is borne out of the anti-GM crop perspective.

Trait Genetic Use Restriction Technology (T-GURT)

The general idea of trait technology is that instead of making embryos non-viable, a particular trait of interest is modified. T-GURT technology uses two main strategies. The first strategy involves a gene construct that is programmed into a seed so that the gene produces the toxin protein that inactivates a particular trait of interest in the plant without killing the embryo. Using this approach, a trait of interest can be selectively silenced by treating the seeds with the chemical inducer before they are sold to farmers so that the targeted trait is absent in the second generation (F_2) [1]. In the second strategy, the gene for the targeted trait is kept silent in the seed but can be activated by the farmer by applying the chemical inducer to the seed any time they want to express the trait in the plant, so farmers are in constant need of the inducer.

Although T-GURT has been developed to make crops more resistant to pests, which would result in higher yields and reduced losses due to pest damage, there are a number of traits of interest. The traits of interest may be herbicide or drought tolerance, pest resistance, seed coat colour, maturity uniformity, etc. However, there is speculation that T-GURT may cause unintended harm to non-target organisms, such as beneficial insects, and has been criticised by environmentalists and organic farmers for its potential impact on the environment and the long-term sustainability of agriculture [3, 14]. However, these are speculations that have not been substantiated. Beyond the science and technology of GURTs, there is a tipping point that involves intricacies of economics, government regulation and consumer issues. However, science also plays a role in the leaning point of adoption. The key is to create a highly efficient GURT system that is environmentally robust and applicable to a range of crops.

Molecular/genetic basis of terminator technology

The molecular basis of GURT involves the use of three different genes with different effects in Terminator technology. Lethal gene: The first gene produces a protein called ribosome-inactivating protein (RIP), also known as the terminator protein. This protein is toxic to the developing seed, so its expression in the embryo inhibits seed germination [5, 8]. Lethal genes cause death when expressed in an organism and have been used in terminator technology to produce non-viable seeds [4]. The lethal gene works with a specific promoter called late embryogenesis abundance (LEA), which, as the name suggests, is active in late embryogenesis, the late stage of seed development after vegetative growth in seed companies' first-generation seeds. To prevent the expression of RIP in F_1, a blocker sequence is usually inserted between the lethal gene and LEA. The lethal gene must be expressed in the second generation (F_2) for a terminator seed to develop, so the blocker sequence that inhibited its expression in F_1 must be removed so that the lethal gene can have direct contact with the LEA promoter. This is achieved by specific site excision, in which the blocker sequence is cleaved at the specific excision sequence (LOX site) by the edges of the blocker sequence [1, 5].

The second gene is the recombinase gene, which encodes a recombinase protein that recognises the excision sequence (*LOX*) and cleaves this sequence together with its blocking sequences from the first gene construct. The most commonly used recombinase excision system is the bacteriophage *CRE/LOX* system, in which the *CRE* protein (recombinase) performs site-specific recombination of DNA at *LOX* sites [1, 13]. The recombinase gene is placed behind a repressible promoter. This promoter is highly specific for a repressor protein, it can be repressed, i.e., the recombinase enzyme is not produced if a particular repressor protein is present. Consequently, the third gene, the repressor gene, produces a

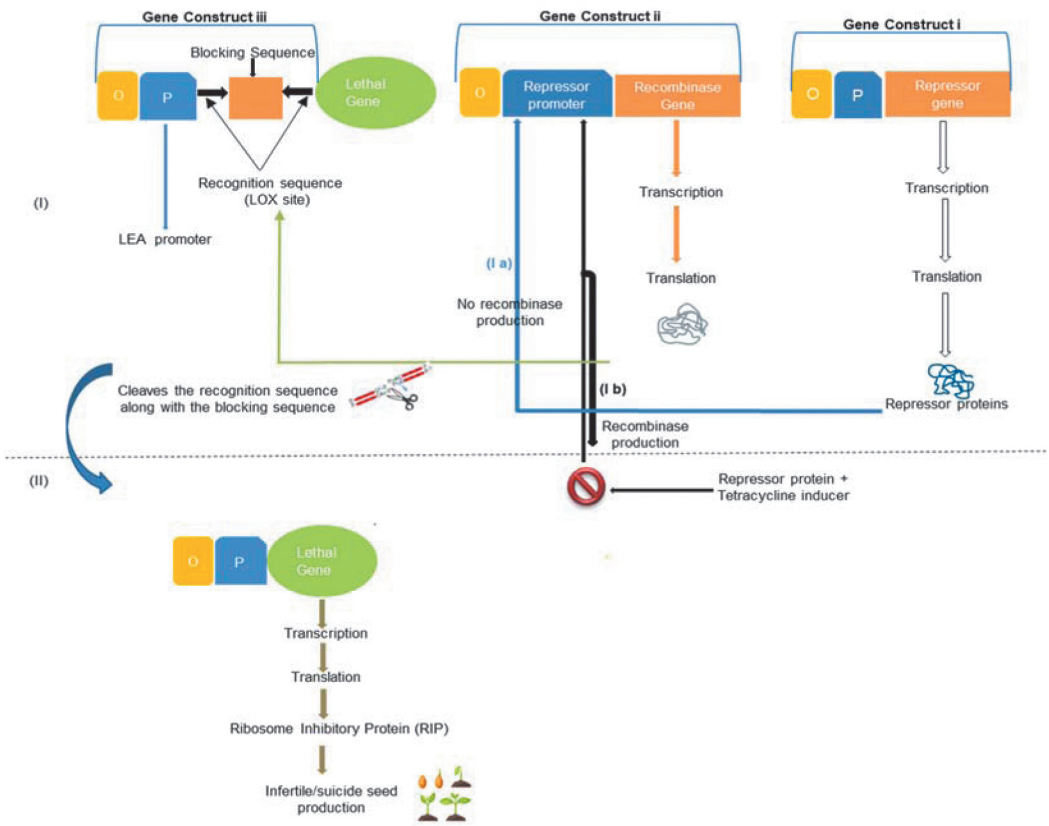

Fig. 1. Genetic basis of terminator technology. The repressor gene in gene construct (i) produces a repressor protein in the absence of the chemical inducer (tetracycline). The repressor protein produced then binds to the repressor promoter in gene construct (ii) to repress/inhibit the production of the recombinase enzyme which prevents the production of the toxic protein (RIP) from the lethal gene, resulting in the production of fertile seeds (as shown in I a and b). However, if the seed companies treat the F1 with the inducer, the inducer will combine with the repressor protein produced in the gene construct (i). This repressor protein-inducer complex prevents the binding of the repressor protein with the repressor promoter in gene construct (ii), thus leading to the production of recombinase enzyme that will cleave the blocking sequence with the help of the excision sequence (LOX site), paving the way for the direct contact of the lethal gene with the late embryogenesis abundance (LEA) promoter, cumulatively leading to the production of the toxic protein (RIP), thus producing suicide seeds (as shown in II).

repressor protein which, when present, inhibits the excision action of the recombinase enzyme and is rendered inactive by the chemical inducer, tetracycline. Now the inactive repressor complex cannot repress/inhibit the promoter attached to the recombinase gene, allowing the synthesis of the recombinase enzyme [5]. Site-specific recombination takes place during germination of the first generation of seeds after sowing; thus, the excision and block sequences are removed from the first gene construct as shown in Figure 1.

Another strategy for terminator technology is the use of a recoverable block of function (RBF) developed in tobacco [15]. This strategy includes a blocking sequence encoding a barnase linked to the gene of interest and a recovery sequence encoding a barstar; a promoter that is only active during seed development, ensuring that the toxin is only produced in the developing seed and not in other parts of the plant. This is expressed under the control of the sulfhydryl endopeptidase (SH-EP) and heat shock (HS) promoters, respectively, all contained in a single insert [13]. Natural expression of the barnase gene in embryos and shoots causes cell death or prevents sexual reproduction of the transgenic plant by blocking mRNA synthesis and germination in the natural environment [1].

The original patent, registered in 1998 and entitled “Control of gene expression” (US Patent 5,723,765), was developed to prevent the unauthorised use of seeds from new crop varieties [16]. Before selling commercial seeds to farmers, seed companies usually treat the seeds with a chemical inducer such as tetracycline [13]. This initiates the process of terminating the viability of the seed. The technology involves three genes with on and off switches [5]. The description of how it works is illustrated in Table 1 and Figure 2.

Pros and cons of genetic use restriction technology

It is clear that GURTs are useful both for technology, intellectual property protection and for limiting gene flow,

Table 1: Basic description of steps involved in Terminator technology to produce sterile seeds.

Terminator genes in the absence of the inducer	Terminator genes in the presence of the inducer
Gene 1: Repressor A repressor gene produces a repressor protein	Gene 1: Repressor The same repressor protein is produced
Gene 2: Recombinase The repressor binds to the binding site and the plant cannot produce the recombinase protein that snips out pieces of DNA.	Gene 2: Recombinase The inducer interferes with the repressor attachment to the binding site, therefore, allowing gene 2 to produce recombinase.
Gene 3: Toxin No recombinase is produced in the absence of the inducer to snip out the blocker. No toxin is produced with the blocker in place hence, by not applying the inducer the seed companies can continue to produce viable seeds	Gene 3: Toxin The recombinase produced from gene 2 helps to snip out the blocker and allows the late promoter to switch on production of the toxin gene late in the season which kills the embryo before the matured seeds are harvested.

Note: A promoter usually drives a recombinase gene. A DNA fragment is inserted between the promoter and the recombinase gene, which is a binding site for the repressor from gene 1: Similarly, a gene for a toxin that is lethal to the embryo, called the 'toxin gene', is controlled by the late promoter (LP), which is only active during the late stage of seed development when the embryo is developing. Between the late promoter and the toxin gene is a DNA insert called a 'blocker', which interferes with the ability of the promoter to switch on the gene.

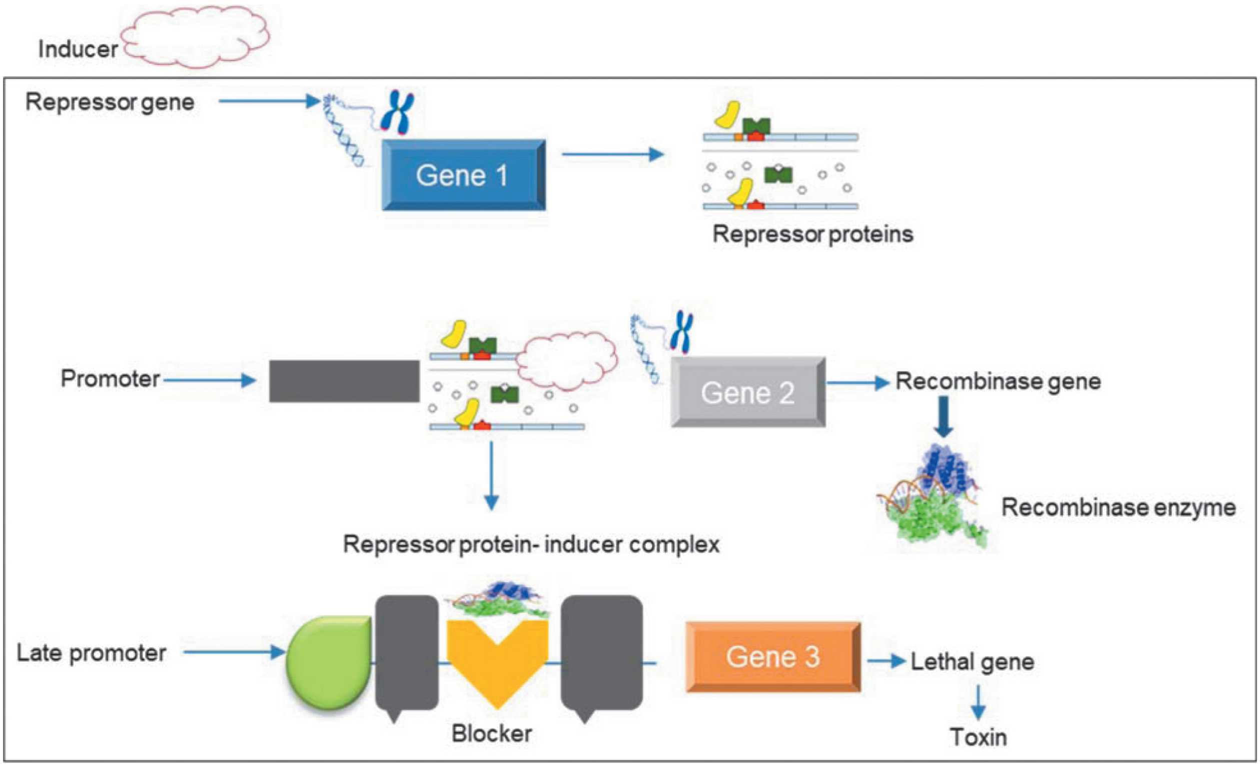

Fig. 2. Tetracycline-induced mechanism of action of the terminator gene. Terminator genes (usually three types: gene 1, gene 2 and gene 3) are inserted into a crop of interest. The seeds are treated with a chemical inducer before being sold to farmers. Gene 1 is a repressor gene, which produces a repressor protein. Gene 2 is the inducer, which interferes with the repressor bound to the binding site, allowing it to produce the recombinase. The recombinase produced by gene 2 helps to cut out the blocker, allowing the late promoter to switch on the production of the toxin gene late in the season, killing the embryo before the mature seeds are harvested.

i.e., for environmental and regulatory reasons. These latter reasons are probably most pressing in the case of next generation "designer" and feedstock crops and other crops where there are particular concerns about gene flow and introgression. There will always be a push-pull dynamic emerging in terms of research and development with the aim of eventually commercialising GURTs. The push is that commercialised GURTs would have tangible regulatory and intellectual property benefits while the pull would likely come from the consumers and regulators, which begs the questions: How safe, and the economic implications of GURTs products? Below, we look at some potential applications and challenges of GURTs.

Containment

According to a study by the International Service for the Acquisition of Agri-biotech Applications [17], containment is one of the main benefits of terminator technology in crop improvement, preventing genetic contamination of non-GM crops. Gene flow is the movement of genes from one population to another and it continues to be a high risk in the context of the biosafety of transgenic crops. The movement of transgenes from the crop to wild relatives and/or weeds remains a concern [4, 18]. GURT can limit the possible spread of transgenes via sexual reproduction from host plants to their relatives, by eliminating the entire genome (V-GURTs) or by removing the transgene from the genome (T-GURTs). Therefore, the use of GURTs could provide additional protection against gene flow and potential unintended consequences that may arise from the use of GM crops. By producing non-viable seeds, terminator technology can prevent the spread of GM traits to non-target plants [11].

Integrated pest management

One of the major constraints in crop production is pest management. Insect pests account for significant yield loss in field crops, and this comes with greater economic burden in their control. Conventional pest control may involve both manual and chemical applications, which are sometime either not effective or not environmentally friendly as in the case of chemical pesticides. In addition to the main purpose of the GURT, the technology could also be used to solve agricultural problems beyond the interests of the holding companies. There are potential applications of GURT in the integrated management of agricultural pests [2]. Crop remnants during the off-season allow the insects to feed and reproduce to maintain a high population level in the next season. The use of GURTs would eliminate the occurrence of volunteer plants from seed lost during harvest or transport and thereby help in pest control. V-GURT technology could also help prevent the spread of fungal spread and disease development by reducing or even eliminating the presence of host plants during the off-season [19, 20]. As a result, it would be an automatic practice for fields sown with V-GURT seeds to be treated with the appropriate hygiene products. In addition to the benefits associated with the reduced incidence of insects and diseases due to the absence of the host, it would also be effective in maintaining the efficacy of transgenic plants.

Hybrid crop production

Another application of terminator technology is the production of hybrid crops. Hybrid crops are created by crossing two genetically distinct parent plants to produce offspring with desirable traits, such as increased yield or disease or abiotic resistance. In other words, a hybrid seed is produced by crossing genetically distinct parent lines to achieve superior traits and heterosis. Hybridisation helps recombine traits to create different varieties, providing a superior assortment of genes. The resulting hybrid seeds are genetically diverse, and the productivity and quality of hybrid crops can be increased [21, 22]. However, in some cases, the resulting hybrid seeds are not stable and do not reproduce the desired traits in subsequent generations. Terminator technology can be used to produce sterile hybrid seeds that can be used for commercial production without the risk of genetic contamination or loss of desirable traits [5].

Intellectual property protection in plant

The use of terminator technology has been controversial, with some arguing that it poses a threat to global food security and farmers' rights. However, others have defended it as a necessary means of protecting intellectual property rights and ensuring continued innovation and development of new plant varieties [6, 7]. In terms of intellectual property protection, terminator technology is primarily used to protect plant breeders' rights (PBRs) and patents. PBRs are a form of intellectual property protection specific to plants and are designed to incentivize plant breeders to develop new and improved plant varieties. Under PBRs, breeders have exclusive rights to control the use of their new varieties for a period of time, typically around 20-25 years [1]. During this time, other breeders are not allowed to produce, sell or use the variety without permission. Patents can also be used to protect plant varieties, although they are less common than breeders' rights in the plant breeding industry. Plant patents are granted to inventors who have discovered or created a new and distinct plant variety and give the inventor the exclusive right to sell, produce and use the plant for 20 years [12]. Terminator technology is particularly useful in protecting breeders' rights because it ensures that farmers cannot save and replant seeds of protected varieties without the breeder's permission. This helps to prevent unauthorised multiplication and distribution of protected varieties and ensures that breeders can continue to earn income from their investment in plant breeding.

While this technology has some potential benefits as elucidated above, it also raises ethical and environmental concerns. Each of these threats is hypothetical, as no such plants have ever been grown and therefore none of them represent actual consequences. The common concern is the permeating government regulation of transgenic plants, which appears to be increasing in stringency around the world. This strictness is paradoxical given the overall environmental and food safety record of transgenic plants. Some of the concerns are discussed below.

Threat to Food Security

One of the main concerns about GURTs is that they could pose a significant threat to global food security. For example, V-GURTs could discourage farmers from saving seeds, a widespread practice in developed countries. This would indeed be a serious constraint in developing countries, particularly in Africa, where smallholder farmers rely heavily on saved seeds for sustainable cultivation and livelihoods. If this technology is adopted in such areas, it could lead to a concentration of power in the hands of a few large seed companies [6]. This could result in seed companies controlling access to the world's food supply, with serious implications for small-scale farmers and food security in many parts of the world. There are concerns that GURTs could have a negative impact on food security and the livelihoods of poor farmers, particularly in developing countries.

Threat to Farmers' Autonomy

Another concern about GURTs is the potential threat to farmers' autonomy. For example, V-GURTs could make farmers dependent on seed companies. In addition, sourcing seeds mainly from GM companies could lead to a loss of agricultural biodiversity and farmers' control over their seeds [23]. T-GURTs could lead to increased use of herbicides with the associated economic burden on farmers. For example, farmers may have to purchase herbicides from the company that developed the crop, reducing their autonomy and increasing their dependence on the company for their weed control needs" [14]. It has been argued that 'terminator' technology could have significant social and economic impacts on smallholder farmers with limited resources, further limiting their ability to expand their crop production. They would have no choice but to buy new seeds every year, which would be prohibitively expensive and counterproductive to sustainable crop production [5].

Threat to Biodiversity

GURTs could also pose a threat to biodiversity. In particular, V-GURTs could lead to the loss of traditional seed varieties with associated negative impacts on biodiversity [4]. The V-GURTs could pose a potential threat to the conservation and sustainable use of plant genetic resources. This is likely to result in the loss of locally adapted varieties and trigger unhealthy competition with landraces and wild types [3]. In addition, the chemical inducers used in terminator technology can degrade the soil, affecting microflora and fauna. As some of the chemicals may contain antibiotics, they can induce the emergence of antibiotic-resistant bacteria and herbicide-resistant weeds, reducing biodiversity and increasing the risk of ecological imbalance and damage [13, 14].

Environmental concerns

In addition to the above concerns, there are also significant environmental concerns associated with terminator technology. One of the main concerns is the potential for gene flow [12, 24]. Gene flow occurs when genes are transferred from one plant to another. This can happen through a variety of mechanisms, including wind, insects and human activity. If terminator genes were to spread to other plants, this could have dire consequences for biodiversity and ecosystem health [25]. As a result, critics of terminator technology argue that it could lead to increased use of pesticides and control of pests and diseases that would normally be controlled by crop rotation and other traditional farming methods. The chemicals used can also have a negative impact on soil fauna and flora [4], soil health, water quality and an increased risk of herbicide-resistant weeds [14]. However, if terminator seeds are engineered to be non-viable at F_1, the possibility of genetic contamination is remote, and until further scientific evaluation proves otherwise, most of the concerns will remain hypothetical dangers that the 'anti-biotech' establishment raises without evidence.

Conclusions

In summary, the technology for restricting the use of genetically modified crops has been developed mainly to protect the intellectual property rights of biotechnology companies and to prevent genetic contamination of non-GM crops. While the technology has some likely benefits, it has also been highly controversial due to concerns about its potential impact on food security, farmers' rights and environmental complications. However, most of the concerns are speculative at best, as no products of the technology have been commercialised. It is therefore essential that the potential risks and benefits of terminator technology are carefully considered before its widespread adoption or rejection. It is important to address the ethical and environmental concerns associated with this technology. Further research and dialogue are essential to decide whether the technology can be used responsibly and in a way that benefits farmers, seed companies and society without unintended consequences. Seed companies must therefore provide farmers with access to non-sterile seeds, promote alternative forms of intellectual property protection, and invest in research to better understand the potential long-term impacts of terminator technology.

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