Türk Bilim ve Mühendislik Dergisi, 3(2): 108-115, 2021

Derleme / Review

Türk Bilim ve Mühendislik Dergisi
Turkish Journal of Science and Engineering

www.dergipark.org.tr/tjse

Interaction between Entomology and Gene Technology: *Bt*-transgenic and Gene Drives for Pests Control

Jean Claude NDAYIRAGIJE [1], **Tuğçe ÖZEK** [1**], **Hacer ÇEVİK** [1], **İsmail KARACA** [1*]

[1]Isparta Uygulamalı Bilimler Üniversitesi Ziraat Fakültesi Bitki Koruma Bölümü, Isparta-Türkiye

*****Sorumlu yazar: ismailkaraca@isparta.edu.tr
**100/2000 YÖK Doktora Bursiyeri

ARTICLE INFO

Received: 28/07/2021
Accepted: 01/12/2021

Keywords: *Bacillus thuringiensis, CRISPR, Plant protection*

ABSTRACT

Pest control is the major agricultural activity for increasing crop productivity thus insuring food security. Recent pest management programs are depending too much on chemical pesticides, which are a threat to our health and environment. One of the greatest entomological achievements for the benefits of plant protection is the use of Bacillus thuringiensis to produce transgenic plants resisting pests. However, such organisms comprise inconveniences against human health and biodiversity in terms of genetic pollution. In many countries, the use of Genetically Modified Organisms is prohibited. This study review on integration of growing gene technology with actual scientific achievements can help to determine a sustainable solution to the pest's problem. In this way, many literatures were referred on to comparatively criticize the effectiveness, safety and sustainability of gene drive over Bt transgenic based on scientific soundness. Gene drive technology is a new technic consisting of gene engineering and on-field monitoring of its transgenes. The case in point is the inappropriateness of Bt-transgenes. Practically, gene drive can be an alternative to Bacillus thuringiensis in pest control for increased safety and environmental protection.

Entomoloji ve Gen Teknolojisi Arasındaki İlişki: Zararlı Mücadelesinde Bt-transgenikler ve Gen Sürücüsüleri

MAKALE BİLGİSİ

Alınış tarihi: 28/07/2021
Kabul tarihi: 01/12/2021

Anahtar Kelimeler: *Bacillus thuringiensis, CRISPR, Bitki koruma*

ÖZET

Zararlılar ile savaş, ürün verimliliğini artırmak ve böylece gıda güvenliğini sağlamak için en önemli tarımsal faaliyettir. Son dönemdeki zararlı yönetimi programları, sağlığımız ve çevremiz için bir tehdit oluşturan kimyasal pestisitlere çok fazla bağımlıdır. Bitki Korumanın yararları için en büyük entomolojik başarılardan biri, zararlılara dirençli transgenik bitkiler üretmek için Bacillus thuringiensis'in kullanılmasıdır. Ancak bu tür organizmalar genetik kirlilik açısından insan sağlığına ve biyoçeşitliliğe karşı sakıncalar içermektedir. Birçok ülkede genetiği değiştirilmiş organizmaların kullanımı yasaktır. Büyüyen gen teknolojisinin gerçek bilimsel başarılarla bütünleşmesine ilişkin bu çalışma, zararlı sorununa sürdürülebilir bir çözüm belirlemeye yardımcı olabilir. Bu çerçevede, gen sürücüsünün Bt transgenikleri üzerindeki etkinliğini, güvenliğini ve sürdürülebilirliğini bilimsel sağlamlığına dayandırarak, karşılaştırmalı olarak eleştirmek için birçok literatüre atıfta bulunulmuştur. Gen sürücü teknolojisi, gen mühendisliğinden ve transgeniklerinin sahada izlenmesinden oluşan yeni bir tekniktir. Buradaki durum, Bt-tansgenikleririn uygunsuzluğudur. Pratik olarak gen sürücü, artan güvenlik ve çevre koruma için zararlı mücadelesinde Bacillus thuringiensis'e bir alternatif olabilir.

1. Introduction

Conventional pest control methods especially chemical insecticides negatively affected human health and environment (Curry, 2002). As of 2014, pesticides were reported to infest 25-77 million workers globally i.e. 1-3% of employees suffered from acute pesticide poisoning while nearly 1 million needed hospital services (Bakhsh et al., 2015). More than this, mismanaged pesticide sprayings induce pesticide resistance thus taking the problem to the worse level. The revolution in gene editing technology is making easier to change genetic materials of organisms with huge potential benefits not only in agriculture but also in other sectors such as healthcare and conservation. Gene technology or gene engineering is a terminology used to mean the technological process for changing the original structure of nucleotides series in a way that generated nucleotide series will significantly encode a desired trait (Taştan & Sakartepe, 2018). Bacteria carrying traits that can harm agricultural pests are being used firstly for exploiting those specific naked genes to transplant them to the genomes of plants. *Bacillus thuringiensis* and *Lactobacillus* were widely used in this context. Secondly, some bacterial genes are used as mediators in transferring important traits with the help of endonucleases like the way CRISPR/Cas9 is being used in gene drive technology

(Dearden et al., 2017). Even though *Bt*-transgenes have provided a huge economic impact worldwide, are not allowed openly in many countries including Turkey. Apart from increased risks to health, an agro political menace may arise in case of licensing *Bt*-transgenes (Aydın et al., 2013). For example, the stability of seeds and food markets as well as quality standards are issued by agricultural politics for both health and economic benefits.

Gene drive can be understood as an experimentally exploitable natural genetic phenomenon. As an entomological division, it consists of two basic principles. The first is the high-precision laboratory gene engineering processes while the other is the scientific modelling of gene drive insect's population after being released to the wild (Esvelt, 2019, Metchanun, 2020 and Alphey et al., 2020). Gene drive is a genetic system with ability to 'drive' itself along within population's genome over many generations (Medina, 2017). Gene drive technology is an applied technic that enhances the inheritance of a modified (or preferred) trait in a specific species (Courtier-Orgogozo et al., 2017). A gene drive is an expression of a genetic element through its ability to statically stay in genetic material of sexually reproducing organism by creating an enzyme which cut both strands of DNA within a targeted area of the genome and make it copied across generations with a self-propagating DNA repair system (RSTA Gene Editing Panel, 2017 and Alphey et al., 2020). Selfishness of gene drives during sexual reproduction is originated from their ability to distort segregation ratios during meiosis or gamete development (Barrett et al., 2019). By definition, a gene drive does not necessitate genetic engineering (Lunshof et al, 2020). There are many examples of naturally occurring gene drives (Esvelt, 2014 & 2019). Alphey et al., (2020) stated many types of gene drive systems existing in nature, for example transposons, sex distorters, toxin-antidote systems, and homing nucleases. There are two types of experimental gene drive. Replacement gene drive is for the case when organism's wild gene is incorporated into gene drive organism to be spread (EFSA GMO Panel, 2020). For example, in mosquito, an anti-parasite transgene was moved into the gene drive mosquito thus rendering it refractory to *Plasmodium* infection or ineffective at its transmission (Metchanun, 2020). The other is suppression gene drive, which targets fertility genes. It employs the method that alter one sex recombinant (for example X-Shredding system) and the population becomes biased on one sex thus reducing reproduction rate (Burt, 2003 and EFSA GMO Panel, 2020). With natural selection rule, genetic residues that can adversely affect health and environment are possible with Genetically Modified Organisms (GMOs) (Saxena & Stotzky, 2000). Actually, organisms with edited genomes present a kind of genetically induced lethality in the wild. After changing any organism's genome for human's benefits, its capacity to survive and reproduce in the wild start depleting and becomes outcompeted by its wild counterparts (Hammond et al., 2016 and Esvelt, 2019). That is the origin of reduced public trust for Genetically Modified Organisms (GMOs) including *Bt*-transgenic and gene drive organisms.

2. Material and Method

This works is a scientific review aiming to discuss the use of Genetically Modified Organisms (GMOs) especially the widely used *Bt* transgenes in comparison with newly growing gene drive transgenic. The research focused on scientific facts especially the limitations of *Bt* transgenic that even caused their restriction in some farming systems and countries whereas gene drive appears as biotechnological science that is showing potentials to resolve the problems of agricultural pests. Reviewed literature was more based on already few published articles and other scientific information. For *Bt* technology is a very old and it's transgenes have used long ago and so many literatures are available. However, many literatures on gene drives are consisting of very new articles, which have examined and discussed more deeply. Moreover, articles on the laboratory application of gene drive and their implications on the effectiveness and sustainability on its field use have focused.

3. Results and Discussion

3.1. *Bt* transgenic

3.1.1. Historical and economic impact of *Bt* transgenes

Bacillus thuringiensis came into use with the 20th century. It was first isolated from the nature by a Japanese biologist Ishiwata Shigotane in 1901. *Bt* had later re-isolated from flour moth caterpillar, *Ephestia kuehniella* in 1911. It was used for the first time as a tool for pest control in 1928 and had first commercialized in France the same year. Since then it was widely used as a biopesticide and later in 1995, the first *Bt* based corn transgenic was produced. Economic Impact of *Bt* crops is very big in some countries as the efficacy of insect resistant crops through *Bt* has been economically certain and are ideally an economic alternative to synthetic insecticides (Bakhsh et al, 2009). The annual market of synthetic insecticides is approximately 8.11 billion US dollars; 30% of these insecticides are applied to vegetables and fruits while 23% and 15% are used to protect cotton and rice, respectively (Bakhsh et al, 2015). The production of *Bt*-cotton resulted into a reduction of 49.8% of insecticide's use worldwide, Mexico and China being at the top with 77% and 65% reductions, followed by Argentina (47%), India (41%), and South Africa (33%), respectively (Qaim, 2009). Turkey would adopt *Bt*-cotton because of its economic importance to its developing domestic textile industry. However, in terms of long-term health and environmental protection, related policies and agro-economic stability were regarded as much more important. In other words, *Bt*-crops are not allowed for growing except the import of maize based poultry feeds (Aydın et al., 2013).

3.1.2. Limitations in adoption of *Bt* transgenes

The deficiencies in *Bt*-transgenes are both scientific and socio-economic based as shown in *Table 1*. They are degradation kinetics of *Bt* proteins, vertical and horizontal gene flow, effects on non-target insects and antibiotic resistance and some other unintended effects. The degradation kinetics of *Bt* proteins occurs after harvest could result in the accumulation and persistence of *cry*-genes (proteins) in the soil due to their binding on soil components. Vertical gene flow consist of the transfer of genes between different organisms but of same species. Seed impurity of varieties may occur as transgenes flow from Genetically Modified to non-Genetically Modified crop (Messeguer, 2003). Zhang et al., (2005) stated that a buffer zone of 60 m could avoid or reduce pollen dispersal from *Bt*-cotton. Londo et al., (2010) announced that the hybrid formation between transgenic *Bt*-crops and wild relatives results in their fitness advantage. Nicolia et al., (2013) declared that this issue must be taken into consideration prior to evaluating the risk of gene introgression to wild relatives. Horizontal gene transfer is when mobile sequences (plasmids, transposons or mobilized chromosomal genes) mediated by bacterial cells are flowing to different species especially those residing in rhizosphere, on plant surfaces and in water (Normander et al., 1998 and Bakhsh, 2015). Effects of *Bt* crops on non-targeted insects are not extreme to predators and pollinators reaching flowers of *Bt*-crops (Losey et al., 1999). One report showed that white flies are much influenced compared to other non-target insects such as lady bugs, wasps etc. (Bakhsh et al., 2015). Antibiotic resistance comes up due to the use of protein markers that help in biotechnical detection of transgenes (Bakshi, 2003).

3.2. Gene Drive

3.2.1. Main areas of application of gene drive technology

Gene drive technology have employed for conservation and ecology, and basic research but it was employed extensively in public health for resolving the problem of vectored diseases and agriculture for plant protection.

In the area of public health, successful gene drive that can prevent disease's transmission could provide a powerful method to eliminate vector-borne diseases such as malaria, which kills nearly 500,000 people, mostly children, every year. Beside malaria transmitted by mosquitoes, many insect-vectored diseases such as dengue, Chagas and Lyme can be prevented from being carried and spread. Gene drive technology can be designed to interfere within a specified point in the genome to knock out a harmful gene. This can allow the vector population to be modified into an anti-parasite transgene, making it resistant or ineffective for transmission of the disease pathogen infection (*Plasmodium* if it is the case of malaria) (Gantz et al., 2015, Hammond et al., 2016, Courtier-Orgogozo et al., 2017, KaramiNejadRanjbar et al., 2018 and Metchanun, 2020). Relevant past decade's researches were aiming to improve the use of CRISPR/Cas 9 for gene drive production and its precision in terms of homing rate or conversion rate toward the wild gene (Gantz & Bier, 2015, Hommond et al., 2016 and Kyrou et al., 2018). Recently, research extension focused on carrying out careful monitoring and modelling of the gene drive transgenic (Metchanun, 2020).

In agriculture, gene drives can be used for pest control by targeting essential genes in their genomes. Until now, there are less or no gene drive pests released but there is a great inclination toward such a subject (Courtier-Orgogozo et al., 2017, RSTA Gene Editing Panel, 2017 and EFSA GMO Panel, 2020). The current approaches were led to pest population suppression in the wild in order to alter organisms that damage crops or the species carrying crop diseases. Anticipated potential entomological uses of gene drive will definitely depend on the extent of researcher's success. For instance, experts are expecting the future use of gene-drive in pest control and much species are being considered as potential targets, from agricultural pests (Perkin et al., 2016, Esvelt, 2016, Courtier-Orgogozo et al., 2017 and Medina, 2017) up to agricultural weeds either by suppression or sensitization (Barret et al., 2019). The most important agricultural pest control method is biological method as the main driver in Integrated Pest Management (IPM). As a practical relationship, Gene Drive and biological pest control may be integrated with *Wolbachia* drive system. According to EFSA GMO Panel (2020), *Wolbachia*-infested insects (drives) can be released to replace actual relative pests. *Wolbachia* are maternally inherited endosymbionts that are capable to manipulate the reproduction of their hosts in many different ways to favour their own maternal transmission. By this, the increase in frequency of females infested with *Wolbachia* is achieved within the target population thus biasing sex ratio. In addition, egg viability is decreased with *Wolbachia*. That endobacterium occurs naturally in a number of insects and have experimentally adopted into others through *Wolbachia* gene drive system by targeting that maternal inheritance trait. Therefore, it is anticipated that by use of *Wolbachia* gene drive system, natural enemies can be adopted as wild counterparts to original pests (EFSA GMO Panel, 2020). The recent improvement in CRSPR/Cas 9 with its great precision allows the recovery of original gene in a case of ecological disruption, and so, we may see its contribution in a very close time.

3.2.2. Ecological Concept of Gene Drive

Gene drive is ubiquitous. Natural occurrence of gene drive is due to the vertical transmission of genetic elements i.e. exclusively from parent to offspring, to reliably increase in frequency within a population even if it cannot help the organism to survive or reproduce as others do (Esvelt et al., 2014). Even though genes might be less expressed to offspring, they are more likely to be passed on to all offspring after biasing inheritance (Lunshof et al., 2020). Esvelt (2016) in his online presentation about gene drive explained that the cow's genome is made up of 25% of rate from snake. This is due to an evolutional gene transfer event mediated by a virus tick that vectored a **jumping gene**, responsible of natural gene drive (a gene introduced in cow from snake that progressively copies itself within genome of cow). Therefore, the origin of natural gene drive is from such useless or broken genes in organism's genome as in every organism, there must be a genome part made of genes with unknown specific responsibility, being around 50% in human.

3.2.3. Experimental Gene drive

Scientists tried to exploit natural gene drive thus producing gene drive transgenes for different benefits (Delborne, 2016). They established different gene drive systems. The first one is homing based drives, which is involved in both suppression and replacement types. It involves CRISPR-Cas9 technology and it is currently the most exclusively trusted in gene drive technology. With help of CRISPR-Cas9, scientists intentionally built self-propagating gene drives within organism's reproductive cells to precisely change traits, alter or suppress various species' population (Courtier-Orgogozo et al., 2017 and Medina, 2017). CRISPR (*Clustered Regularly Interspaced Short Palindromic Repeats*), a family of DNA sequences naturally found in the genome of prokaryotic bacteria is not a very old discovery**.** CRISPR system is experimentally organised set of tools including the DNA strand containing the trait of interest, endonuclease enzymes such as Cas9 or Cas12 and guide RNA that both work together as a package to deliberately govern biochemical reactions in a reproductive cell of a given organism. They actually work with great precision but genomic impurities are possible according to the defined platforms (DeFrancesco, 2015). As other gene technology applications, any genetically modified organism to take place and to be officially released must have a synergic interaction between its molecular, cellular, and organismal and ecosystem processes as stated in the work of Barrett et al, (2019). For gene drive, even if the earliest proposals to develop them rose with the 20th Century the molecular tools were lacking until the discovery of CRISPR/Cas9. The CRISPR/Cas9 technology for gene editing is around 10 years old (Courtier-Orgogozo et al, 2017). It employs a couple of endonucleases including transcription activator-like effector nucleases (TALEN), zinc finger nucleases (ZFN) and Cas9-guide-RNA constructs hence called sometimes nuclease-based drives (Taskan & Sakartepe, 2018; Barret et al, 2019 and EFSA GMO Panel, 2020). It spread very fast in the wild with increased resistance allele's generation rate. In addition, reversibility is higher as compared to other designed systems. It was employed extensively with *Drosophila*, *Saccharomyces*, *Anopheles stephensi* and *Anopheles gambiae* (Champer et al., 2016). Apart from homing based drives, there are also X-shredder also known as driving-Y systems or sex-linked meiotic drive system, which is a suppression gene drive. Y chromosome in the modified male mosquito was designed to damage the X chromosomes in the germline (Champer et al., 2016 and Metchanun, 2020). Toxin-antidote under-dominance drive system, which is a replacement gene drive. This drive system employs the combination of toxin and antidotes in order to produce underdominance (Confinement) (Champer et al., 2016 and EFSA GMO panel, 2020). There is *MEDEA (maternal-effect-dominant-embryonic-arrest)* drive system, which is a replacement type gene drive (Champer et al., 2016, Barret, 2019 and EFSA GMO panel, 2020). There is Chromosomal rearrangement producing replacement type gene drive (Champer et al., 2016). There is *Wolbachia* Drive System that is used to produce replacement gene drive (Champer et al., 2016 and NEA, 2021).

3.2.4. How does gene drive cheats inheritance?

Gene drive inheritance occurs through sexual reproduction but its mechanism is completely different from normal (Mendelian) inheritance. Normally, the offspring inherits two versions of every gene, one from each parent with half probability (50:50) that each particular variant of the gene will be transmitted. Thus, its frequency remains constant in the population (Delborne, 2016 and Alphey, 2020). In gene drive inheritance, if one set of chromosomes contains a 'gene drive'; it cuts the partner chromosome that lacks the gene drive and copy itself onto this chromosome. Therefore, gene drives expression ensures that a certain gene will be usually expressed, with almost a 100% of chance, but depending on gene drive system and its mechanism nature. This allows the variant to spread rapidly through a population to encode a desired trait (Delborne, 2016). Gene drive is not applicable with the use of bacteria as it is done in *Bt*-transgenes because it has to be transmitted exclusively from parents to offspring and this mode of reproduction is not common for bacteria.

3.2.5. Key factors for a gene drive program

According to Delborne (2016), various factors influence gene drive propagation. The "**evolutionary fitness**": individuals carrying the gene drive should have adequate ability to produce fertile offspring as compared to individuals not carrying the gene drive. The "**conversion rate**": which describes how the gene drive is passed to subsequent generations when one parent carries the gene drive and the other does not. The "**gene flow**": which describes how the gene drive moves between different populations of the target species. The "**horizontal gene transfer**" or the potential for gene drives to move from the target species into entirely different species.

Other important elements are very imperative especially during wild propagation and monitoring of gene drive. They include first "**fitness cost**": it is the effort of organism's population to survive anti-evolutionary factors. It is mostly important in suppression type gene drives where important genes for survival (for non-developing offspring) or reproduction of the target population (fertility reduction, sex ratio biasing toward males) are influenced (Buchman et al, 2018). In addition, fitness cost is involved by introducing a gene drive for reducing organism's lifespan. The "**Self-sustenance and self-limitation of a gene drive":** Some gene drives involve drive genes that progressively increase in frequency in a target population and ideally become stable after some generations. They are mostly used in a condition that spatially unrestricted gene drives are required and include CRISPR-Cas9 based drives (Gantz et al., 2015 and EFSA GMO Panel, 2020). Whereas self-limiting drives employ drive genes that will limitedly spread in period of time or within a limited area (EFSA GMO Panel, 2020). That is caused by the gradual reduction in its frequency over a limited number of generations and are outcompeted by wild counterparts (Esvelt et al., 2014 and Marshall & Akbari, 2018). The "**gene drive markers**": They are genes that may help to biotechnologically track gene drive organisms in their habitat because gene drives need monitoring and temporarily and spatially can escape confinements (DiCarlo et al., 2015). The "**technical efficacy**": It is the measure of how similar the gene drives will be spread in wild compared to how they spread during laboratory trials. The "**gene drive threshold**": it is the rate of organisms (% of the target population size) that will be released into the wild in order to achieve the intended level of gene drive spread. Below that threshold, gene drive distinct in early generation before it become spread (EFSA GMO Panel, 2020). The gene drive threshold is determined by fitness cost and gene flow pattern because they are not readily estimated during laboratory experimentation. Therefore, it helps not only in measuring drive's efficacy but also in determining the probability of gene drive flow in non-targeted populations (Lunshof et al., 2020).

3.2.6. Mechanism of experimental gene drive

The mechanism of a standard gene drive technology i.e. without caring on which kind of template gene or drive system must involve the following stages to produce self-propagating gene drive. The first stage is the laboratory instruction for gene drive elements propagation. It refers to the identification of the important gene and Recoding important gene to build DNA cassette (Esvelt, 2016; 2019). The DNA cassette contains three elements being the gene encoding the bacterial Cas-9 protein (enzyme), a gene coding a guide RNA that targets a particular site in the genome and the flanking sequences which allow the cassette to insert at a given target site (Gantz & Bier, 2015, Hammond et al., 2016 and Courtier-Orgogozo et al., 2017). Then the CRISPR system is built by supplementing DNA cassette and required endonucleases. The second stage is a self-propagation of drive system in laboratory**.** It generally involves first the matching and cutting of the DNA's target site in wild genome. The second is the DNA cleavage to allow a drive construct replacing the wild gene with a drive gene on the allele. Later the generated DNA is repaired and then copied in order to form homology of drive. Remember that gene drive is transmitted through sexual reproduction in its meiotic phase. This allows the gamete to receive instructions from doing genome editing on its own. In this way, every single gene drive transgenic mating with a wild organism give rise to the gene drive transmission (Alphey, 2020). The last stage is the release of gene drive organism and monitoring of its spread in the wild. Default expectation in a standard gene drive program is that the gene drive is likely to spread in the wild.

In experimental gene drive, precision measure is important as it determines potential risks. The homing rate and the ratio of Homology Directed Recombination to Non-Homologous End-Joining are the measures of experimental precision. After the CRISPR-Cas9 system is applied in gene drive technology, two forms of results that have to determine the success of the process are possible (Esvelt et al., 2014). The important gene on DNA strand has to be successfully copied as a strict copy by responsible endonucleases. That is technically called *homologous recombination*. In contrast, some mechanisms may not involve full precision where parts of separate genes can recombine only under the directive of active sites but this also includes impurities (Champer et al., 2019 and Barrett et al., 2019). This is called *non-homologous end joining* and is considered a disrupted gene (Esvelt et al., 2014, RSTA Gene Editing Panel, 2017 and Esvelt, 2019). Mosquitoes of either homozygous or heterozygous drive transgene presented 10% higher mortality rate than wild-type mosquitoes (Selvaraj et al., 2020).

There are theoretical statements that gene drive can cause regional or even global extinction of some pests. This is provisional to self-sustaining or global gene drives (Steinbrecher & Wells, 2019). Restoration of wild type gene in population replacement drive is possible. Nevertheless, this can be trusted when homing rate is complete because the wild-type version of the sequence will be pure when edited gene by the gene drive is excluding off-target sequences. The addressing of this issue had researched exclusively in the laboratory by use of the system of a reversal gene drive (DiCarlo et al., 2015). This can be supported of the fact that some researches shown that homing rate depletes with generations. Hommond et al., (2016) found the homing rate of 91.4 - 99.6 % in early generations, which reduced to 69 % in late generations. The resistance tested was in-frame mutation, means the possibility of a mutation in a targeted genome. In addition, homing rate varies according to the used cell i.e. can be less in eggs while being more in male gamete (Gantz et al., 2015).

3.2.7. Current gene drive governance status

Governance is a domestically and/or internationally existing hierarchical and authoritative framework for a given program (Kelsey et al., 2020). Within that framework, a number of regulations have to be mutually and democratically agreed upon or approved by a central authority after being collaboratively developed. Whereas the above said regulations should comprise all necessary collective ethical, socio-economic, political, environmental, health and safety values and concerns especially in scientific works under growth like gene drive. Governance structure in terms of federal level, either democratic, monarchy or constitutional) impose the formal process of regulations and laws issued by administrations and local governments. By now, there is no formal governance or process of regulation of gene drive technology and the release of gene drive insects on international level (Lunshof et al., 2020). This is very problematic, as policy undermines existing innovative approaches to improving the gene drives by allowing conflicts between scientific integrity and institutional interests. Therefore, universal gene drive governance must be in place to foster conditions under which new technologies can be sustained (Kelsey et al., 2020).

Bt transgenes have adopted of economic crops that cannot be physically consumed such as cotton (Aydın et al., 2013). The fact that they are so problematic to health and environment (as shown in Table 1) make it so logical since genetic pollution must avoided for public health benefits. The remaining issues for environmental protection them created the limitation for wide use of *Bt* transgenes in many countries including Turkey. Whereas the limitations in gene drive are not based on their effects to environment (RSTA Gene Editing Panel, 2017). In other words, the serious challenges in gene drives are not scientific dependent but more related to socio-political considerations (Dearden et al., 2017 and Esvelt, 2019). According to Courtier-Orgogozo et al., (2017), gene drive organisms are called wild GMOs because are expected to act exclusively in the wild. Gene drives works better for pests that reproduce sexually and that have short generation times (Esvelt, 2019). This goes in accordance with the point that in agricultural pest management, pests reproducing so quickly are the most threatening. On the other hand, other potential pests are economically damaging throughout the whole year with big life span and long reproduction cycle. In this way, the latest gene drive technology is not yet suitable for all pests and needs expansion.

Table 1. Mean cutting parameters of plant stalk in tests with a smooth knife

No	GMOs risks and negative effects	Specific Source	Bt/GMOs	Gene Drive/GMOs	Comparative Comments
A			**Scientific**		
1	Food safety problems	-Allergenicity, -Antibiotic resistance	**V**	**X**	Not necessary to consume gene drive GMOs differently to *Bt* crops.
2	Horizontal and Vertical gene flow due to Bt toxins in ecosystem.	Genetic residues' bioaccumulation causing unintended gene flows.	**V**	**X**	*Bt*-technology is less specific as Bt-genes can flow through plasmids etc. while gene drive is only transmitted sexually with 100% specificity.
3	Development of pesticide resistant weeds and insects.		**V**	**v**	It is more likely in *Bt*-transgenes, but less likely in the gene drives unless the rate of development is slow.
4	Risks for non-target organisms	Reduced specificity for Bt-toxins	**V**	**X**	*Bt*-toxins can kill non-targeted species (Lövei et al., 2009) whereas gene drives are sexually spread and different species or strains are essentially not inter-fertile. In addition, targeted species may be suppressed together with their traits of important ecological service (in a case of polyploidy). However, it is not common for gene drives hence are limited.
5	Health and biological system damage and loss of natural ecosystem services	Degradation kinetics and unintended genetic pollutions	**V**	**v**	
6	Targeted species disintegration or extinctions (Medina, 2017, Esvelt, 2019)	Due to population suppression or knock out	**-**	**v**	Impossible for *Bt*-transgenes and less likely in gene drives when it is a global drive because gene drive is actively reversible and limited in space and time (Esvelt et al., 2014 & Steinbrecheret al., 2019).
7	Ride along	Due to accidental insertion of a given gene into a gene drive	**-**	**V**	This is particular to gene drive.
B			**Socio-Economical**		
8	Unintended market problems	Brand value degradation due to reduced social trust	**V**	**V**	Both Bt-transgenes and Gene drive still experience lack of public trust in terms of consumption (varying with sates, cultures, social views)
9	Potentially high exposure to compensation liability	In case of health and environmental damage	**V**	**V**	Both Bt-transgenes and Gene flow have to guarantee for any side effects that may degrade health and ecosystem.

Given the gene drive transgenes against agricultural pests, when the project concerned is designed with adequate specificity and precision, the pests may remain harmless in the wild and possibly without any contact with humans. The following are the raisons why wild GMOs should be adopted. Natural selection act by eliminating altered and/or unfit genes. However, this is provisional for genes that are governed by basic rules of inheritance. Among genes that do not obey these rules and expected ratios of allele's expression to offspring as in Mendelian Genetics are therefore used for gene drives (Esvelt, 2019). Gene drives are natural and ubiquitous (Delborne, 2016 and Esvelt, 2019). This make them safer and much more stable not to be confused with other GMOs. Gene drive organisms are supposed not to be consumed and are less likely come into significant interaction with health. Easy to be produced, to be evaluated, to be anticipated of consequences and to be controlled by modelling. Gene drive propagation in wild population is a relatively slow and reversible process. Recent technological advance renders gene drives with no genetic pollutants and toxic residues (when homing rate is 100%) (Kyrou et al., 2018 and KaramiNejadRanjbar et al., 2018). Economic (cheap), fast, accurate and efficient (Courtier-Orgogozo et al., 2017). Delborne, (2016) declared in their seminar paper, gene drive program as a whole should employs different sciences including gene drive research, values with ethics, governance, public engagement, risk assessment and phased testing. Gene drive application deserves to be applied on harmful or threat organisms in order to reduce risks to health and ecosystem.

Another approach in entomological applications for agricultural pests is that gene drive may be used to increase the susceptibility to plant's defensive biochemical molecules. Gene drives could be used to eliminate pesticide resistance (Esvelt et al., 2014). Medina (2017) states that the fact that pesticide resistance is already a consequence of wrong human intervention, using gene drive for eradication is a non-logical. Here, the fact that not all pesticides are safe in different degrees support that a gradual elimination of pesticide use in agriculture is definitely a big advantage. Apart from a sustainable plant protection that can be provided by the coverage of gene drive population on a wide area, produced crops can be of quality and may not be subjected to pesticide residue controls. May be some pests which do not play a critical ecological role may be interfered in their reproduction genes to be altered using gene drive (Burt, 2003). Insects such as thrips are completely harmful in ecosystem because are physically damaging and transmit viral diseases. Such pest's interests to colonize agricultural crops can be attenuated thus remaining on wild plants. Whereas viral disease transmission trait can be prevented by adopting the immunity trait of a pest to host that pathogenic virus. According to Barret et al., (2019), gene drive can be readily exploited to control weeds. Two elementary ways can be followed. The first being to suppress weed's population and secondly to sensitize weed populations.

Targeting natural enemies is probably the last priority choice. However, some natural enemies can be supplemented of traits that enable them to repel pests. As example, wild pollinators can be provided of a trait encoding biosynthesis of repellents for thrips control. Insecticides have been being applied frequently and natural enemies have threatened due to pesticide's side effects or reduced specificity to pests (El-Wakeil et al., 2014). Gene drives could protect natural enemies and other ecologically important insects such as bees by making them resistant to such pesticide's active ingredients. However, gene drive technology is not ensuring the safety and conservation of targeted insects. Targeting one or two charismatic or beneficial species will not be an ideal solution (Delborne, 2016, Medina, 2017 and Barrett et al., 2019). Thus, implementation of this strategy should only be allowed in situations in which pesticide effects are extreme and gene drive is relatively improved.

4. Conclusion

Many debates have extensively executed about GMOs especially *Bt*-crops and taken decisions have been always bipolar. This is because their disadvantages are more important against both health and environment. Whereas gene drive is a fast growing field and scientists are focusing on relevant last issues. According to our study, gene drives present less cues compared to other GMOs and their scientific applicability guarantee effectiveness when adopted particularly for pest control. Based on scientific soundness, gene drive may be much more suitable to be adopted and disseminated for pest control compared to *Bt*-transgenes (Table 1). However, a serious problem is its poor regional and lack of universal governance making it publicly not famous and low trusted. Many developing countries, farming systems and agricultural policies are captive to social concerns and this low flexibility has led to incompatibility with recently rapidly growing technologies such as gene drive. We agree with many researchers, regulators and other decision-makers who recommend that the reliance upon a "reversal" gene drive as the sole strategy for mitigating the effects of gene drive is worse than choosing safe gene drive platform. It is required to establish universal gene drive governance (as stated above) for wise dissemination this technic not only for public health protection but also for agricultural pest control. As the technology will be rendering gene drive status adequately safe, another important issue will be to improve the social trust by allowing criticism on social, cultural, legal and economic implications of revolutionary gene-drive technology.

Conflict of Interest

The article authors declare that there is no conflict of interest between them.

Authors' Contributions

The authors declare that they have contributed equally to the article.

5. References

Alphey, L.S., Crisanti, A., Randazzo, F. F., & Akbari, O. S. (2020). Opinion: Standardizing the definition of gene drive. *Proceedings of the National Academy of Sciences*, *117*(49), 30864-30867.

Aydın, C.İ., Özertan, G., & Özkaynak, B. (2013). Assessing the GMO debate in Turkey: The case of cotton farming. *New Perspectives on Turkey, 49*, 5-29.

Bakhsh, A., Khabbazi, S. D., Baloch, F. S., Demirel, U. Çalışkan, M. E., Hatipoğlu, R., Özcan, S., & Özkan H. (2015). Insect-resistant transgenic crops: retrospect and challenges Insect-resistant transgenic crops: retrospect and challenges. *Turkish Journal of Agriculture and Forestry, 39*(4), 531-548.

Bakhsh, A., Rao. A. Q., Shahid. A. A., Husnain, T., & Riazuddin, S. (2009). Insect resistance and risk assessment studies in advance lines of *Bt* cotton harbouring *Cry1Ac* and *Cry2A* genes. *American-Eurasian Journal of Agriculture and Environmental Science, 6*(1), 01-11.

Bakshi, A. (2003). Potential adverse health effects of genetically modified crops. *Journal of Toxicology and Environmental Health, Part B, 6*(3), 211-225.

Barrett, L.G., Legros, M., Kumaran, N., Glassop, D., Raghu, S., & Gardiner, D.M. (2019). Gene drives in plants: opportunities and challenges for weed control and engineered resilience. *Proceedings of the Royal Society of B, Biological Science, 286,* 1-9. https://doi.org/10.1098/rspb.2019.1515

Buchman, A., Marshall, J.M., Ostrovski, D., Yang, T., & Akbari, O.S. (2018). Synthetically engineered *Medea* gene drive system in the worldwide crop pest *Drosophila suzukii*. *Proceedings of the National Academy of Sciences of the United States of America, 115*, 4725-4730.

Burt, A. (2003). Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proceedings of the Royal Society of B, Biological Science, 270*, 921-928.

Champer, J., Buchman, A., & Akbari, O.S. (2016). Cheating evolution: engineering gene drives to manipulate the fate of wild populations. *Nature Reviews-Genetics. Macmillan Publishers Limited, 17*(3), 146-59.

Courtier-Orgogozo, V., Morizot, B., & Boëte, C. (2017). Agricultural pest control with CRISPR-based gene drive: time for public debate. Should we use gene drive for pest control? *Science and society. EMBO report, 18*(6), 878-880.

Curry, D. (2002). Farming and Food: A Sustainable Future. *Report of the Policy Commission on the Future of Farming and Food. London, UK: Her Majesty's Stationery Office*: 90-92.

Dearden, P.K., Gemmell, N. J., Mercier, O. R., Lester, P. J., Scott, M. J., Newcomb, R. D., Buckley, T. R., Jacobs, J. M. E., Goldson, S. G., & Penman, D. R. (2017). The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand, 48*(4), 225-244.

Delborne, J.A. (2016). Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. *National Academies of Sciences, Engineering, and Medicines*, *358*(6367), 1135-1136. DOI: 10.1126/science.aap9026

DeFrancesco, L. (2015). Gene Drive Overdrive. *Nature Biotechnology, 33*, 1019-1021.

DiCarlo, J.E., Chavez, A., Dietz, S.L., Esvelt, K.M., & Church, G.M. (2015). Safeguarding CRISPR-Cas9 gene drives in yeast. *Nature Biotechnology, 33*(12), 1250-1255.

El-Wakeil, N., Gafaar, N., Sallam, A., & Volkmar, C. (2014). *Side effects of insecticides on natural enemies and possibility of their integration in plant protection strategies.* Insecticides-Development of Safer and More Effective Technologies. (Ed. Stanislaw Trdan, İnsecticides), InTech, 548. http://dx.doi.org/10.5772/54199.

Esvelt, K.M. (2016). Openly engineering our ecosystems.*TEDxCambridge*. Online Presentation. https://www.youtube.com/watch?v=eoRqivhO6NM&t=487s.

Esvelt, K.M. (2019). Gene drive. *MIT.* Online Presentation. https://www.youtube.com/watch?v=7X715cD02sA&t=157s.

Esvelt, K.M., Smidler, A.L., Catteruccia, F., & Church, G.M. (2014). Emerging technology: concerning RNA-guided gene drives for the alteration of wild populations. *Elife, 3*: e03401.

EFSA (European Food Safety Authority) Panel on Genetically Modified Organisms (GMO). (2020). Evaluation of existing EFSA guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified insects with synthetically engineered gene drives. *European Food Safety Authority Journal, 18* (11), e06297. doi: 10.2903/j.efsa.2021.6301

Gantz, V.M., Jasinskiene, N., Tatarenkova, O., Fazekas, A., Macias, V.M., Bier, E., & James, A.A. (2015). Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*. *Proceedings of the National Academy of Sciences in U.S.A*, 112(49), 6736-6743.

Gantz, V.M., & Bier, E. (2015). The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science, 348*(6233), 442-444.

Hammond, A., Galizi, R., Kyrou, K., Simoni, A., Siniscalchi, C., Katsanos, D., Gribble, M., Baker, D., Marois, E., & Russel, S., Burt, A., Windbickler, A.C., Crisanti, A., & Nolan, T. (2016). A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. *Nature Biotechnology,* 34(1), 78-83.

KaramiNejadRanjbar, M., Eckermann, K.N., Ahmed, H.M.M., Sánchez, C.H.M., Dippel, S., Marshall, J.M., & Wimmer, E.A. (2018). Consequences of resistance evolution in a Cas9-based sex conversion-suppression gene drive for insect pest management. *Proceedings of the National Academy of Sciences of the U S A, 115*(24), 6189-6194.

Kelsey, A., Stillinger, D., Pham, T.B., Murphy, J., Firth, S., & Carballar-Lejarazu, R. (2020). Global Governing Bodies: A pathway for gene drive governance for vector mosquito control. *The American Journal of Tropical Medicine and Hygiene, 103*(3), 976–985.

Kyrou, K., Hammond, A.M., Galizi, R., Kranjc, N., Burt, A., Beaghton, A.K., Nolan, T., & Crisanti, A. (2018). A CRISPR-Cas9 gene drive targeting double sex causes complete population suppression in caged Anopheles gambiae mosquitoes. *Nature Biotechnology, 36*, 1062-1066.

Londo, J.P., Bautista, N.S., Sagers, C.L., Lee, H.E., & Watrud, L.S. (2010). Glyphosate drift promotes changes in fitness and transgene gene flow in canola (*Brassica napus*) and hybrids. *Annals of Botany 106*(6), 957-965.

Losey, J.E., Rayor, L.S., & Carter, M.E. (1999). Transgenic pollen harms monarch larvae. *Nature, 399*, 214-215

Lövei, G.L., Andow, D.A., & Arpaia, S. (2009). Transgenic insecticidal crops and natural enemies: a detailed review of laboratory studies. *Environmental Entomology 38*(2), 293-306.

Lunshof, J., Shachar, C., & Edison, R., & Jayanti, A. (2020). Technology Factsheet Series: Gene drives. *Belfer center for science and international affairs.* Available on: belfercenter.org/TAPP.

Marshall, J.M., & Akbari, O.S. (2018). Can CRISPR-based gene drive be confined in the wild? A question for molecular and population biology. *ACS Chemical Biology, 13*(2), 424-430.

Messeguer, J. (2003). Gene flow assessment in transgenic plants. *Plant Cell, Tissue and Organ Culture, 73*, 201-212.

Metchanun, N., Borgemeister, C., von Braun, J., Nikolov, N., Selvaraj, P., & Gerardin, J. (2020). Role of gene drives in an integrated malaria elimination strategy in high burden countries: modeling impact and cost-effectiveness in the Democratic Republic of the Congo. *MedRxiv preprint server for health sciences*.

Medina, R.F. (2017). Gene drives and management of agricultural pests. *Journal of responsible innovation, 5*, 255-262.

NEA (National Environmental Agency). (2021). Using male Wolbachia-carrying Aedes aegypti (Wolbachia-Aedes) mosquitoes to reduce the dengue mosquito population. *Wolbachia-Aedes* mosquito suppression strategy. *Singapore Government Agency website*. https://www.nea.gov.sg.

Nicolia, A., Manzo, A., Veronesi, F., & Rosellini, D. (2013). An overview of the last 10 years of genetically engineered crop safety research. *Critical Reviews in Biotechnology, 34*(1), 77-88.

Normander, B., Christensen, B.B., Molin, S., & Kroer, N. (1998). Effect of bacterial distribution and activity on conjugal gene transfer on the phylloplane of the bush bean (*Phaseolus vulgaris*). *Applied and Environmental Microbiology, 64*(5), 1902-1909.

Perkin, L.C., Adrianos, S.L., & Oppert, B. (2016). Gene disruption technologies have the potential to transform stored product insect pest control. *Insects, 7*(3), 46. https://doi.org/10.3390/insects7030046

Qaim, M. (2009). The economics of genetically modified crops. *Annual Review of Resource Economics, 1*(1), 665-693.

RSTA (Royal Society Te Apārangi) Gene Editing Panel. (2017). The use of gene editing to create gene drives for pest control in New Zealand. *Royal society of the New Zealand*.

Saxena, D., & Stotzky, G. (2000). Insecticidal toxin from *Bacillus thuringiensis* is released from roots of transgenic *Bt* corn in-vitro and in-situ. *FEMS Microbiology Ecology, 33*(1), 35-39.

Selvaraj, P.P., Wenger, E.A., Bridenbecker, D., Windbickler, N., Russell, J.R., Gerardin, J., Bever, C.A., & Nikolov, M. (2020). Vector genetics, insecticide resistance and gene drives: An agent-based modelling approach to evaluate malaria transmission and elimination. *PLOS Computational Biology 16*(8), e108121

Steinbrecher, R.A., & Wells, M. (2019). Gene Drives, a report on their science, applications, social aspects, ethics and regulations. *Critical Scientists Switzerland (CSS), European Network of Scientists for Social and Environmental Responsibility (ENSSER) and Vereinigung Deutscher Wissenschaftler (VDW).*

Taştan, C., & Sakartepe, E. (2018). CRISPR Genom Modififikasyonları T101. *Researchgate*. PhD Thesis.

Zhang, B.H., Pan, X.P., Guo, T.L., Wang, Q.L., Wang, Q.L., & Anderson, T.A. (2005). Measuring gene flow in the cultivation of transgenic cotton (*Gossypium hirsutum* L.). *Molecular Biotechnology, 31*, 11-20.