

Gene Drives and International Trade:

An Analysis of World Trade Organization Rules and
Their Governance of Ecosystem-Altering Organisms

by

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B.S. Environmental Science
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Submitted to the Institute for Data, Systems, and Society
in partial fulfillment of the requirements for the degree of

Master of Science in Technology and Policy

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2019

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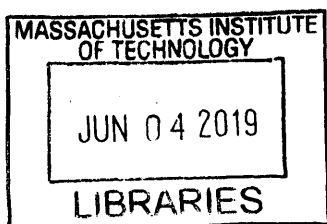
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Abstract

The development of self-propagating gene drive containing organisms may have wide-reaching consequences, including for international trade. Given compelling potential applications in disease mitigation and pest management, countries may develop and release these self-propagating products of biotechnology in the near future. Such products will cross international borders through natural organism movement and through trade, potentially altering not only the populations and ecosystems of the country that developed the product, but also those of the countries to which they spread. Political and economic consequences will arise, some of which the World Trade Organization (WTO) will govern. The WTO's Agreement on Sanitary and Phytosanitary Measures (SPS Agreement) is an especially pertinent set of trade rules which permits trade restrictions aimed at protecting the health of a country's citizens or other species only when scientific evidence supports the perception of risk to the health of citizens or other species. In the early 2000s, the WTO evaluated the SPS Agreement for applicability to genetically modified crops, but no such analysis has yet been completed for gene drive containing organisms. In this thesis, I first summarize the status of gene drive development, highlighting divergent techniques and their status in laboratory experiments. I then explore potential scenarios for trade disputes involving gene drive containing organisms, with differing technological and ecological specifications. I examine the text of the SPS Agreement, as well as its past application to trade disputes, to evaluate relevance to gene drive containing organisms. Finally, I formulate suggestions to policy makers and technology developers for preventing international disputes on, and disruption of trade by, gene drive containing organisms.

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Acknowledgements

I would like to first thank my advisor Kevin for your willingness to take on an unconventional student, for your insight and candor, and for the significant flexibility you provided, without which my studies would not have been possible. Thank you to Ken Oye for helpful feedback on this thesis and to you and Amy Porges and for useful discussions that helped me grasp the functioning of the (largely mysterious) WTO. Thank you to Sam Weiss Evans for sharing your thesis and experiences, and to both you and Jeantine Lunshof for your kindness and guidance throughout my studies. Thank you to Frank Field for the many hours you spent patiently helping me wrap my head around what it meant to be a TPP student and what a TPP thesis was. Thank you to Barbara DeLaBarre for your continuous support and endless empathy that helped me through many difficult moments during the last two years.

I can never describe the depth of my gratitude to my family, friends, and partner Ryan, not only for making my Masters possible, but also for making my life exceptional. My parents have sacrificed their entire lives to give their children every opportunity, and I find time and again that there is no limit to their generosity, kindness, support and humor. I am extraordinarily lucky to have parents like you, who, no matter their own trying circumstance, would never stop facilitating their children's success. Thank you to my Dad for always finding the exact words to get me through self-doubt and despair, and for your visits that were bright spots in many hard weeks of my semesters. Thank you to my Mom for being the most tireless advocate for me, and for the dedication that you have shown to my education my entire life, upon which this incredible opportunity was built. Thank you to my sister, Katie, for being just the right person to look up to and learn from, even though you never seem to grasp the extent of my admiration for you, and to both you and Steve for sharing your expertise and care whenever I needed it. Thank you to Molly for your inexhaustible optimism and support, and for never letting the three-hour time difference get in the way of our conversations, which always do me so much good. Thank you to Brian and Chris, for being a reliably funny and fun retreat from life's hardships, and for still liking me through our nine-year-old friendship. Thank you to Grace and Nette for your camaraderie and validation, for laughing through the pain with me, and for always being ready to vent over ice cream. Thank you to Ryan for being my rock, for making our home happy and full of love even in the hardest of times, and for making me laugh every single day.

Introduction

Justification and purpose

Gene drive is a phenomenon in which a genetic element becomes inherited by offspring at high frequencies and reliably spreads throughout a population, regardless of its benefit to organisms. This selfish genetic behavior can occur in diploid organisms, which include all plants and animals. Diploid organisms have two copies of each gene, and may be heterozygous, meaning that they possess one allele, or version, of a gene on one chromosome and a different allele on the other. One form of gene drive occurs when one allele manipulates cell machinery to copy itself and replace the other allele, making the organism homozygous (having two copies of one allele) instead of heterozygous and biasing inheritance such that all of that organism's offspring will have the copied allele. This particular example of the larger gene drive phenomenon is, confusingly, most often referred to simply as "gene drive". Scientists have been aware of these natural systems for decades, and were studying and attempting to manipulate them since the 1940s (Min et al. 2018). Many theorized that we could engineer organisms that contain gene drive systems with a human-selected trait, hereafter referred to as "gene drive containing organisms", in order to alter many members of a species. Only since the discovery of Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR, however, has this idea been practically feasible. As Esvelt et al. (2014) first described, CRISPR can be used to create a type of man-made gene drive by inserting CRISPR genes into organisms alongside the gene you hope to spread. Compelling applications of gene drive containing organisms include elimination of vector borne illnesses, humane suppression of pests and invasive species, and fortification of threatened species. Several groups are currently developing gene drive containing organisms with the hope of realizing these benefits.

Significant risks are also associated with the development of gene drive containing organisms. While the technology development is occurring in laboratories, the products would exist in natural environments, with complex and poorly understood dynamics. These genetic systems may affect the species they alter in unforeseen ways, especially in combination with environmental forces. The altered organisms may disrupt ecosystems, causing effects which may be impossible to predict from laboratory testing. Perhaps most acutely, gene drive containing organisms will almost certainly cross regional and international borders, entering territories of people who did not develop them and who may not consent to their presence or effects. Given existing disagreements and tensions over genetic modification, political and economic responses to such border crossings could be momentous.

An internationally coordinated response to gene drive technology has not yet been achieved. In the absence of a recognized international forum for the determination of the ethics and safety of new

technologies, international institutions with other missions, such as the World Trade Organization (WTO) and the United Nations (UN), are often the home of these discussions. The UN discusses gene drives in the context of its Convention on Biodiversity, which aims to preserve ecosystems, species, and genetic resources for equitable and sustainable human benefit (Convention on Biological Diversity 1992). The convention has repeatedly considered a moratorium on gene drive release (Callaway 2016; Callaway 2018) but currently allows for cautious project progression (Achenbach 2018).

We expect that in the future, the WTO will likewise consider gene drive technology. International differences in perception of the safety or ethics of new technologies have on numerous occasions come to a head at the WTO as countries challenge the ability of other countries to trade those technologies. News sources frequently report on popular controversies that become international trade disputes. For example, the safety of genetically modified crops (Schalch 2003), morality of online gambling (Pimlott 2007), ethics of flavored cigarettes (Miles and Palmer 2012), safety of high proof alcohols (Gruszczynski 2016), and safety of hormone treated beef (Miles 2017) have each been debated at the WTO. Questions about gene drive containing organisms can be expected to similarly play out in WTO dispute settlements. Furthermore, international trade would facilitate the spread of gene drive containing organisms, since all current development projects are in insects or rodents: species that are routinely, though inadvertently, spread through trade of other goods (Bradshaw et al. 2016; Yue, Lee, and Wu 2017).

International trade disputes, though routine, are highly consequential. Preparation for and, if possible, avoidance of disputes over gene drive containing organisms may help reduce the negative political and economic consequences of this technology. This preparation may also help ensure that potentially beneficial uses can be undertaken where appropriate and popularly supported. To these ends, our research aimed to assess the range of impacts this technology might have and understand how it may relate to existing rules and systems. In this thesis, I anticipate scenarios in which a trade disputes may occur as a result of the release of gene drive containing organisms, and explore how the WTO may resolve these disputes. Before this, however, a review of the status of this technology and a description of the WTO are necessary.

Types of gene drives & status of development

To date, no gene drive containing organisms have been released. Several research groups within nonprofits and universities are known to be developing gene drives to address selected human health or environmental concerns. These projects differ in their specific approach to gene drive technology, and in

their status of technology development. I categorize these projects based on each group's publications; the feasibility of their claims was not assessed.

Gene drive development can be categorized along two axes: geographical scope and goal. The geographical scope of a gene drive development project can either be global or local. Global gene drives can persist indefinitely and could spread to each member of a species worldwide, while local gene drives spread only to a small area around the site of organism release because of a design modification. The goal of the project can either be suppression or alteration. Suppression gene drives limit the reproductive ability of the organism in order to reduce the population size of the altered species, while alteration drives spread a characteristic but do not affect population size. In a tabular representation (see Table 1 below), four quadrants characterize the locations projects can occupy along these two axes: global suppression, global alteration, local suppression, and local alteration.

The groups listed in each quadrant of Table 1 are leading each of the known major gene drive development projects. I also characterize their status of development into one of four stages that would occur before release into the wild. The first stage occurs outside of the laboratory; some institutions publish their plans for constructing a gene drive, with theoretical mechanisms often supported by computer models, before beginning laboratory experiments. The second stage is laboratory testing in individuals, wherein the gene drive sequence is inserted into individuals from the altered species' genomes and tested for desired effect. The third stage is laboratory testing in populations, in which gene drive containing individuals are released into a wild type, or unmodified, population to study how the drive propagates and long-term stability of the construct. The final stage before gene drive containing organisms would be released into the wild involves field trials. Many institutions would want to study how these organisms perform in natural environments before a general release, and field trials in isolated locations, such as islands where the altered species is not present, offer a controlled, limited scope, opportunity to do so. Model results, however, suggest that global gene drive systems would be highly invasive, with a mere handful of organisms sufficing to invade new populations, and implying that any field trial of a global gene drive system would be equivalent to a global release (Noble et al. 2018). As of this thesis, no known project has begun field trials. The known projects occupy one of the first three development stages, as displayed in Table 1.

		Geographical scope	
		global	local
Goal	suppress	<ul style="list-style-type: none"> • Target Malaria 	<ul style="list-style-type: none"> • Pirbright Institute • UCSD • GBIRD • MIT
	alter	<ul style="list-style-type: none"> • UCSD • UCI 	<ul style="list-style-type: none"> • MIT

Key:

- Theory/model only
- Lab testing individuals
- Lab testing in populations
- Field trials

Table 1. Development status of known, major gene drive projects. Projects are populated along two axes: geographical scope and goal.

Target Malaria is the only known project conducting lab tests in populations, and is thus the project in the furthest stage of development. Funded by the Bill & Melinda Gates Foundation, Target Malaria is a non-profit research consortium working with universities and stakeholders and evaluating several approaches to reducing the number of female *Anopheles gambiae* mosquitoes, which transmit malaria, in sub-Saharan Africa (Target Malaria 2019). While the project is also exploring alteration traits that could make mosquitoes resistant to malaria or make them unable to bite humans, their most advanced work is in global suppression drives. They have developed a high-security testing facility in Terni, Italy, where they are analyzing how quickly their trait of biased sex inheritance spreads throughout populations (Stein 2019). The group is currently testing multiple techniques, including engineering males to produce mostly male offspring and engineering individuals to produce sterile female offspring. Early experiments testing the former strategy indicate that the spread of the drive and the resulting population sex-ratio distortion were both significant but fell short of model predictions (Facchinelli et al. 2019). Laboratory results testing the viability of the latter technique met or exceeded model predictions (Kyrou et al. 2018).

The Pirbright Institute is a research institute in the United Kingdom which studies diseases of livestock. A research team there is evaluating two types of local suppression gene drives for *Aedes aegypti* mosquitoes, which transmit many diseases to humans and animals. Both systems, underdominance and killer-rescue, are understood to be threshold-dependent, meaning that they would not propagate in a population until the genetic construct reaches a threshold frequency. If gene drive containing organisms crossed into a territory where other gene drive containing organisms had not been released, the gene drive

is predicted to be eliminated by genetic drift and natural selection, limiting the alteration to the geographic area of release (Edgington and Alphey 2018). The Pirbright institute has published multiple mathematical models of these gene drives, but no laboratory results.

Genetic Control of Invasive Rodents, or GBIRD, is a non-profit research consortium investigating the use of local suppression drives to reduce invasive rodent populations on islands (GBIRD 2017). Invasive rodents reduce biodiversity and transmit diseases, and their effects are most pronounced on islands. One GBIRD research team at North Carolina State University is testing sex ratio-biasing global suppression gene drive (NCSU n.d.). They aim to limit their drive systems to specific islands by locating the drives in alleles that are ubiquitous on those islands but rare on the mainland. Their models suggest that these drive systems would still spread through but not suppress mainland populations (Sudweeks et al. 2019).

Two gene drive development projects are being conducted by a research group at the University of San Diego (UCSD). One project, funded by the California Cherry Board, aims to locally suppress *Drosophila suzukii*, a major agricultural pest that lays eggs in ripening fruit. The group has developed a system, which they call *Medea*, that biases inheritance for gene drive propagation through toxin-antidote coupling in a threshold-dependent manner. Recent research observed successful inheritance bias for several generations but apparent resistance was developed after generation six. Future research aims to address this resistance and to identify appropriate transgenes to incorporate into the engineered gene drive (Buchman et al. 2018). The other project is developing a global alteration drive which makes *Aedes aegypti* unable to transmit Zika virus. The group has successfully engineering an introduced gene, or transgene, that reduces the rates the mosquitoes can be infected with the virus, and may eliminate their ability to transmit the virus. They have not yet incorporated this transgene into a gene drive system (Buchman et al. 2019).

At the University of California Irvine (UCI), a research team is developing a global alteration drive in *Anopheles stephensi*, an Asian mosquito species that transmits malaria. They have identified genes that prevent infection and are testing a drive delivery system (Gantz et al. 2015).

The Sculpting Evolution group at Massachusetts Institute of Technology (MIT), of which I am a part, is developing localized alteration drives for use in several gene drive applications. Using the model organisms *Caenorhabditis elegans* and *Mus musculus*, they are testing the feasibility of a self-exhausting system called “daisy drive”. Constructed by splitting up the components of the gene drive onto different chromosomes, daisy drives are expected to spread and persist in populations for only a limited number of generations until they are eliminated by natural selection (Noble et al. 2019). This transient nature is

expected to also limit the geographical spread of the drive, rendering Daisy drives appropriate for transient, local applications. The group is considering the implementation of Daisy drives for the immunization of rodents against ticks to reduce Lyme disease prevalence, should their ongoing non-drive genome editing project succeed (Buchthal et al. 2019). They are also developing components of daisy suppression drive systems in rodents. Additionally, motivated by concerns about the evolutionary stability and regulatory approval of gene drives, they are developing non-drive suppression systems that could potentially address the same objectives with fewer social implications.

World Trade Organization

The World Trade Organization was created in 1995. It expanded upon and modernized the scope of its predecessor, the General Agreement on Tariffs and Trade (GATT), which had been in place since 1947. Both the GATT and the WTO were created to protect free trade and to allow trade disputes to be resolved in a peaceful manner, rooted in the desire to avoid repeating the horrors of the Second World War (World Trade Organization n.d.). There are 164 countries that are members of the WTO, and 22 countries that observe (World Trade Organization 2016). Research indicates that the WTO has largely been successful in its promotion of trade. Both member countries and observing countries trade substantially more than countries that do not participate in the WTO (Goldstein, Rivers, and Tomz 2007). By one estimate, the WTO has more than doubled international trade (Subramanian and Wei 2007).

There are two primary activities of the WTO: to create trade agreements that outline rules of trade established by consensus, and to settle disputes when governments believe other members are violating the terms of trade agreements (World Trade Organization 2018).

Trade responses to the release of gene drive containing organisms would likely be considered in the context of the Agreement on Sanitary and Phytosanitary Measures (SPS Agreement). The SPS Agreement went into effect with the creation of the WTO in 1995, and concerns measures adopted by countries that aim to protect the health of their citizens and other species. Such measures restrict trade through regulation of imported products, and include blocking certain types of products, limiting which locations may import products, and inspecting or treating products before they enter the country. The SPS Agreement allows such measures when they help ensure the safety of consumers or limit the spread of diseases and pests, but strictly dictates when and how countries may impose them (World Trade Organization 1998a).

The WTO is a reactive, rather than proactive, organization. The agreements they set are written to reflect the issues of the time, and are infrequently updated. The WTO does not advise countries on how new technologies may be governed by their agreements. Instead, disputes must occur before the organization will interpret these innovations. In the context of gene drive technology, this may be undesirable. Once released, global gene drives will rapidly spread, and social and ecological effects may accumulate during the time it takes to initiate and resolve a trade dispute. As such, the following evaluation of how the SPS Agreement applies gene drive technology may aid efforts by technology developers and policy makers to anticipate and avoid negative consequences from these products.

Methods

To understand the potential trade consequences of gene drive containing organism development, I identified scenarios of interest by considering the potential range of technological and ecological circumstances and assessing the political and economic importance of each.

To then predict how, in these identified scenarios, trade disputes over SPS measures that prevent the spread of gene drive containing organisms may be resolved at the WTO, I analyzed two sources of information. First, I examined the text of the SPS Agreement. I identified the critical components of the agreement which dictate when measures are permissible, and explored the relevance of gene drives to those components. Second, I analyzed prior decisions made by the WTO on SPS measures.

There have been 48 complaints brought to the WTO over SPS measures. These cases begin as requests for consultations by one country, the complainant, against another, the respondent. If consultations do not resolve the dispute, member countries convene as the Dispute Settlement Body (DSB). The DSB establishes a panel to hear the case and issue a report, upon which DSB decisions are made. The DSB has issued decisions on 19 of the disputes involving SPS. I examined all 48 disputes and 19 decisions, and further analyzed cases I determined to be of particular relevance to gene drive containing organisms as case studies.

Results

Scenarios of interest

If gene drive containing organisms were to be released, countries may impose trade-disrupting measures that fall under the SPS Agreement. Several potential scenarios, with unique technological and ecological circumstances, are of interest.

In the scenarios that follow, allow Country A to represent a country that authorized the development and release of a gene drive containing organism product, and Country B to represent a country that, in response, has imposed a trade restricting measure on imports from Country A. The species to which the gene drive containing organism belongs will be referred to as the “altered species.”

Four characteristics define each scenario of interest: whether the gene drive is global or local; whether the gene drive is suppressive or altering; whether the altered species is present in Country B; and, if the altered species is present in Country B, whether the altered species is of importance, here used to mean a species native to the ecosystem or a non-pest species or both, in Country B. These characteristics are expected to be most relevant to trade disputes. As described above, gene drives can be global or local, and suppressive or altering, with each combination of these having a different consequence for the altered species and, presumably, the ecosystem. Whether or not the altered species is present in Country B may be highly consequential. All of the known gene drive development projects aim to alter species that are present in more than one country, and some, such as rodents, are present nearly worldwide. It is therefore probable that at least one country that is home to the altered species may oppose gene drive release. However, Country B may wish to prevent the entry of gene drive containing organisms even when the altered species is not present, either due to concern about the product’s ecological effects, or because of the potential for the gene drive to spread to related species that are present, or because of moral opposition to the technology. Whether or not the altered species is an alien or pest species in Country B may likewise be important. Countries are more likely to wish to block gene drive containing organisms when the species is of importance there, however, concern for ecosystem effects or moral opposition may motivate action even if the altered species is a pest.

The following 12 scenarios illustrate all combinations of these characteristics, as illustrated in Table 2. In Scenario 1, the gene drive containing organism was engineered with a global suppression drive, and the altered species is present and of importance in Country B. In Scenario 2, the gene drive containing organism was engineered with a global suppression drive, and the altered species is present but not of importance in Country B. In Scenario 3, the gene drive containing organism was engineered with a global

suppression drive, but the altered species is not present in Country B. In Scenario 4, the gene drive containing organism was engineered with a global alteration drive, and the altered species is present and of importance in Country B. In Scenario 5, the gene drive containing organism was engineered with a global alteration drive, and the altered species is present but not of importance in Country B. In Scenario 6, the gene drive containing organism was engineered with a global alteration drive, but the altered species is not present in Country B. In Scenario 7, the gene drive containing organism was engineered with a local suppression drive, and the altered species is present and of importance in Country B. In Scenario 8, the gene drive containing organism was engineered with a local suppression drive, and the altered species is present but not of importance in Country B. In Scenario 9, the gene drive containing organism was engineered with a local suppression drive, but the altered species is not present in Country B. In Scenario 10, the gene drive containing organism was engineered with a local alteration drive, and the altered species is present and of importance in Country B. In Scenario 11, the gene drive containing organism was engineered with a local alteration drive, and the altered species is present but not of importance in Country B. In Scenario 12, the gene drive containing organism was engineered with a local alteration drive, but the altered species is not present in Country B.

Scenario	Geographical scope		Goal		Altered species present in B		Altered species important in B	
	Global	Local	Suppression	Alteration	Yes	No	Yes	No
1	✓		✓		✓		✓	
2	✓		✓		✓			✓
3	✓		✓			✓		
4	✓			✓	✓		✓	
5	✓			✓	✓			✓
6	✓			✓		✓		
7		✓	✓		✓		✓	
8		✓	✓		✓			✓
9		✓	✓			✓		
10		✓		✓	✓		✓	
11		✓		✓	✓			✓
12		✓		✓		✓		

Table 2. Potential scenarios in which Country A releases a gene drive containing organism and Country B responds with an SPS measure.

Of these twelve scenarios, some are of greater concern or more immediate likelihood than others. Given the comparative ease of generating a global gene drive as compared to a local gene drive, Scenarios 1

through 6 are more likely to occur in the immediate future. These scenarios are also more likely to generate significant political and trade responses than scenarios 7 through 12, since global drives are inherently broader reaching. The gene drive project in the most advanced stage of development aims to suppress the altered species, and furthermore more applications may exist for the suppression of pests, pathogens, or vectors than for the alteration of species, indicating that Scenarios 1 through 3 may arise first. The most advanced project aims to alter *Anopheles gambiae*, which is present regionally in sub-Saharan Africa but not globally, indicating that Scenarios 1-3 are all conceivable in the short term. However, creating a suppression drive that persists despite considerable evolutionary pressure for individuals to evolve resistance, and technical challenges may lengthen the timelines of these projects. Scenarios 3 through 6 are therefore also possible as the first trade disputes about gene drives.

Because the first gene drive containing organisms released will likely be global, and because of the greater likelihood of political opposition to global gene drives, Scenarios 1 through 6 were chosen as the focus for the remainder of this analysis.

Text of the agreement

The SPS Agreement outlines when SPS measures are allowable, and how countries must implement allowable SPS measures. The following analysis was conducted on the text of the agreement published on the WTO website in 1998.

SPS measures are defined as those aimed at protecting human, animal or plant life or health, within the territory of the Member, from the entry, establishment, or spread of pests, diseases, disease-carrying organisms or disease-causing organisms (Annex A). Measures can include relevant laws, degrees, regulations, requirements, or procedures which may, directly or indirectly, affect international trade (Annex A; Article 1.1).

The following features of the SPS Agreement, summarized in Table 3, are most relevant to gene drive containing organisms. Members are permitted to impose SPS measures when they are necessary for the protection of the life or health of a country's humans, animals, or plants. Permitted measures must be based on science and justified with sufficient scientific evidence (Article 2.2). They may not unjustifiably discriminate between members, and cannot be used to disguise other motivations for restricting trade (Article 2.3). Members must harmonize their measures with international standards where they exist and may only impose measures with stricter protections when they have sufficient evidence (Article 3.1). When assessing risks, they must consider risk assessment techniques developed by relevant international

organizations, and take into account scientific evidence as well as the prevalence of the disease or pest in question, relevant ecological conditions, and economic consequences of entry of the disease or pest (Article 5.2, 5.3). When there is not enough relevant scientific evidence, members may adopt provisional SPS measures using the existing information while obtaining the necessary information for a more objective assessment of risk within a reasonable period of time (Article 5.7). Members must be transparent in their imposition of SPS measures, and must aim to minimize negative trade effects (Article 7, 5.4).

Section	SPS measures	Considerations for application to gene drives
Article 2.2	Must be based on science; must be justified by scientific evidence	Evidence on risks may not exist by time of dispute
Article 2.3	Must not unjustly discriminate between members; must not disguise other motivations for restricting trade	Imposed measures would have to be placed on all countries with gene drive containing organisms
Article 3.1	Must harmonize with international standards where they exist	International standards may not exist by time of dispute
Article 5.2, 5.3	Must consider recognized risk assessment strategies; must consider specifics of product and ecologies	Risk assessment may be challenging before product release
Article 5.7	May be adopted provisionally while more information on risks is obtained	Measures could be imposed before information on risks is available
Article 7, 5.4	Must be imposed transparently; must be written to minimize negative trade effects	Measures could not be imposed that cause more than necessary trade disruption

Table 3. Relevant sections of the SPS Agreement, requirements these sections impose for trade-restricting measures and considerations for the application of those sections to gene drive containing organisms

Given these requirements, SPS measures may be justified in several of the scenarios of interest. For Scenarios 1 and 2, in which global suppression drives are generated by Country A in a species that is present in Country B, SPS measures would likely be justified. By definition, suppression drives are a threat to the life of members of the altered species, and measures imposed by Country B to prevent their entry would meet the requirements of allowable SPS measures. Such measures may be more likely to be imposed in Scenario 1, given the importance of the altered species to Country B, however they may also be imposed in Scenario 2 if Country B is concerned that the alteration of pest species could cause wider ecosystem effects.

The application of the SPS Agreement to Scenarios 4 and 5 is more complex. Alteration of the altered species may be considered a threat to the health of the altered species, depending on conceptions of health. While alteration drives may or may not interfere with the overall wellbeing of the altered species, for which there is no clear metric, the evolutionary fitness of altered individuals will almost certainly be reduced relative to unaltered counterparts. Human-introduced genes are generally thought to confer at least a small disadvantage to an organism, since energy is diverted away from survival and reproduction towards expression of the human-introduced trait. For instance, the UCSD laboratory group developing a global alteration drive to make *Aedes aegypti* unable to transmit Zika found the introduced gene lowered female longevity and reduced the number of eggs that hatched, but did not impact other metrics of fitness such as mating success or wingspan (Buchman et al. 2019). To the extent that evolutionary fitness is encompassed within conceptions of animal and plant health, further analysis on the fitness cost of gene drives may be necessary.

In Scenarios 3 and 6, in which the altered species is not present in Country B, SPS measures imposed to protect the altered species would be unlikely and nonsensical. Instead, Country B might impose SPS measures aimed at protecting other species that are present in their areas. Should they justify those measures with concern for potential direct or indirect effects that gene drive containing organisms could have on humans or other species, it is less obvious how the text of the agreement may apply. Impacts of gene drive containing organisms on other species within and among ecosystems has yet to be assessed, and will be challenging to study before a product is released.

For all scenarios, it is relevant that the text of the agreement does not indicate that trade restricting measures may be imposed only on the products of concern, rather than on products that spread the products of concern. It is therefore conceivable, albeit unprecedented, that a country's measure that blocks a given import out of concern for its spread of another product would be consistent with the rules outlined by the SPS Agreement. For instance, should a country wish to prevent the entry of insect gene drive containing organisms and to that end impose trade restricting measures on produce, with evidence that insects are spread through the trade of produce, that may be permissible under this agreement.

Prior decisions

Of the more than 500 trade disputes brought to the WTO in its history, 48 have involved the SPS Agreement (World Trade Organization 2019). Case summaries, complainant or respondent

documentation, and panel reports were obtained for analysis from the WTO website.

The 48 cases involving the SPS Agreement were analyzed for trends in decision making. Figure 1A illustrates the split of decisions. The DSB formally resolved only a subset, issuing decisions on 19 of the 48 cases. Of the remaining 29, nine were settled outside of DSB, while the other 20 have no WTO listed resolution. When the DSB did issue a decision, it favored the complainants in all except two cases. In each of these 17 cases favoring complainants, respondents' measures were found inconsistent under their SPS Agreement obligations and instructed to become compliant. In the two cases that favored the respondent, no such change was mandated.

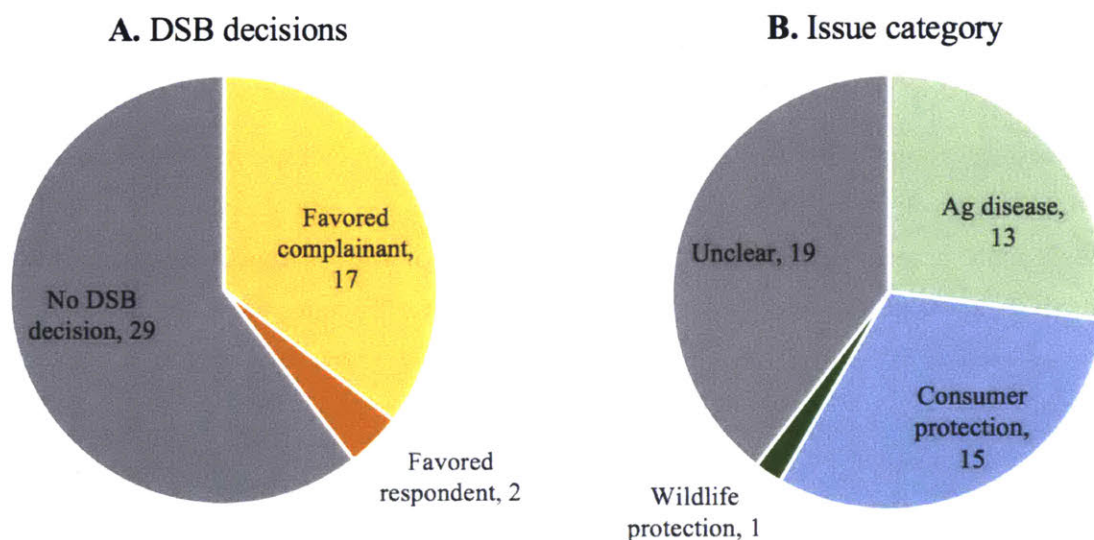


Figure 1. Prior disputes involving the SPS Agreement. **A:** DSB decisions for each of the 48 prior cases involving SPS. “Favored complainant” indicates that the DSB found the respondent to be in violation of their obligations and required corrective action. “Favored respondent” indicates that the DSB did not find the respondent to be in violation of their obligations and required no corrective action. “No DSB decision” indicates that the dispute was resolved outside of DSB or that the dispute remains open with no resolution. **B:** Type of issue the contested measure aimed to address for each of the 48 prior cases involving SPS. “Agricultural disease” includes cases where the contested measures aimed to prevent the spread of diseases of crops or agricultural animals. “Consumer protection” includes cases where the contested measures aimed to prevent harm to humans consuming the imported products. “Unclear” includes cases where the issue was not able to be determined from available documentation.

When possible, I identified the issues that were at the center of each debate. The SPS Agreement is sufficiently broad in its language that relevant measures could include any that attempt to preserve the life or health of a species in that country. The majority of cases, however, involved measures aimed at protecting agricultural species of animals or crops or at protecting human consumers. For many of the

cases for which there was no panel report or DSB decision, it was impossible to determine which issues the contested measures aimed to address. These results are displayed in Figure 1B.

These statistics indicate two key characteristics of WTO disputes that involve SPS measures. First, measures that restrict trade in the name of protecting species infrequently are upheld by the DSB. In the two cases in which the DSB favored the respondent, the contested measures aimed to protect consumers from the effects of radionuclides and asbestos, each of which had been established as carcinogens by the time of the dispute, 2015 and 1998 respectively (Environmental Protection Agency 1992; Bartrip 2004). Contested measures in the 17 cases in which the DSB favored the complainant aimed to protect against, among other things, avian flu, foot and mouth disease, fire blight, and hormones in food products. While DSB decisions often emphasize procedural, rather than scientific, justifications, it is suggestive of the high standard to which SPS measures are held that only measures blocking known human carcinogens have been upheld.

Second, contested measures almost always aim to protect either agricultural species or humans, with only one case on record involving the wellbeing of a wildlife species. In that case, the contested measure involved quarantine of imported salmon to protect wild salmon populations from diseases, and may have been as motivated by concerns for domestic fishing supply as it was by concern for wildlife wellbeing. The available record of the DSB decision making in disputes over the protection of wildlife is therefore limited.

Importantly, the dispute record for SPS Agreement measures also indicates that these events typically last years, and many find no formal resolution at the WTO. For the 19 instances in which the DSB issued a decision, there was an average of 3.3 years between the start of the dispute and the DSB panel's report, with the longest case taking 6.5 years. For the 9 cases that were resolved outside of DSB, the resolution was reached on average 1.5 years after the start of the dispute, with the longest case taking 3.9 years. For the remaining 20 cases in which no resolution has been reached, 15 were initiated at least 5 years ago, and seven were initiated more than 20 years ago. Timelines for cases that have reached a conclusion are displayed in Figure 2.

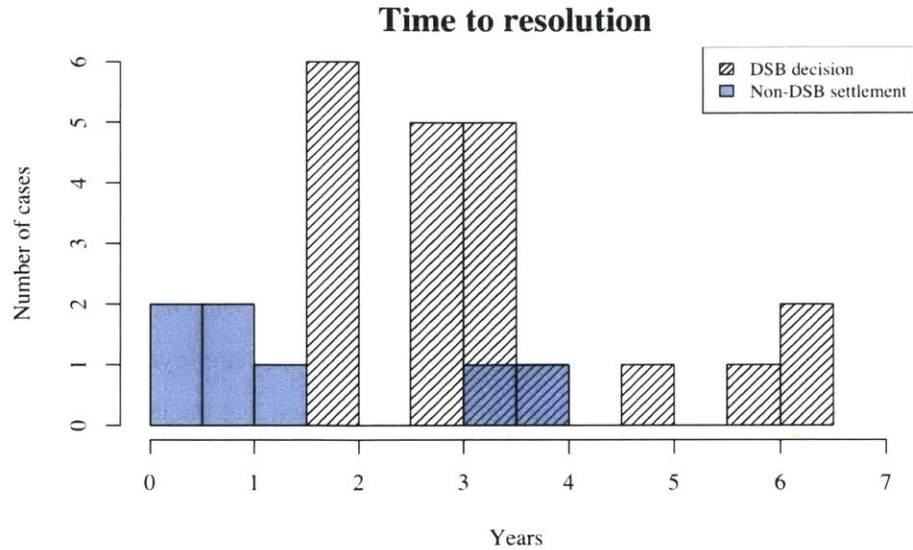


Figure 2. Time to resolution displayed for cases for which there was a formal DSB decision in black diagonal lines and cases for which a non-DSB settlement was reached in blue.

In the case of gene drives, this long delay between the submission of a complaint and the achievement of a resolution may be especially consequential. During the course of a multiple year dispute, a gene drive could spread as gene drive containing organisms reproduce, with the extent of proliferation dependent on the generation time of the altered species. While the trade-blocking measure imposed by Country B may largely prevent the entry of gene drive containing organisms into their territory, the gene drive may enter other countries during the course of the dispute. Some of those countries may be tracking the dispute in order to incorporate the WTO decision into their own policies on this technology, and the lengthy process may complicate their ability to set definitive policies.

Given these characteristics, it is evident that SPS measures aimed at preventing the entry of even atypical products such as gene drive containing organisms would have to meet a high standard in order to be upheld. Scenario 1, in which Country A develops a global suppression drive in an altered species that is both present and important in Country B, is the most likely scenario in which an SPS measure would be upheld because it represents a significant threat to Country B's species and ecosystem. In Scenarios 2 and 3, which differ from Scenario 1 in that the altered species is not important or not present, respectively, in Country B, the justification for a measure may rely on potential for ecological disruption or gene drive spread to other species. Data is unlikely to exist on the evaluation of these concerns at the time of a trade disruption, and as such measures may be viewed as overly cautious and unjustified. In Scenarios 4 through 6, an SPS measure may not be upheld since alteration may not be considered a serious threat to the species in Country B.

Case study: genetically modified crops

One prior SPS dispute is particularly relevant for prediction of conflicts over gene drive containing organisms. In 2003, the United States, Canada, and Argentina each submitted requests for consultation with the European Union (European Communities at the time of the dispute) over two aspects of EU rules regarding genetically modified crops. First, the EU had not approved any agricultural biotechnology products for sale or cultivation since 1998. Second, the EU had in place safeguard measures which allowed individual member states to restrict EU-approved products if the state had evidence of risk to human health or the environment, which several European countries had employed to restrict EU-approved genetically modified crops. Each of the complainants alleged that the lack of approval of products, which amounted to a moratorium, and the safeguard measures were in violation of the EU's responsibilities under the SPS Agreement. When consultations failed to resolve the dispute, a panel was established to consider the complaints of all three complainants together in one case.

The complainants argued that the EU moratorium and safeguard measures violated the SPS Agreement because they were without scientific basis, not transparent, and not executed without undue delay. The EU argued that their actions were consistent under the SPS Agreement because their lack of approval did not constitute an SPS violation by itself, domestic products had been treated the same as imported products, and there was no evidence of a moratorium. As Evans (2004) described, in the course of their arguments the US emphasized the benefits of genetically modified crops and framed the matter as an issue of trade, while the EU emphasized risks and framed that the matter as an issue of safety regulation.

In 2006, the DSB panel released a report, finding the EU to be in violation of its responsibilities under the SPS Agreement. The lack of approval of any agricultural biotechnology product since 1998 amounted to a de facto moratorium and violated Article 8 and Annex C(1)(a) by having undue delay for an approval procedure. Additionally, the panel found that the safeguard measures violated Article 2.1 and Article 5.1 of the SPS Agreement because they were not sufficiently supported with scientific evidence and were not based on satisfactory risk assessments. The DSB adopted the panel's report, and in December of 2006 the EU agreed to implement the recommendations and rulings (World Trade Organization 2010).

This dispute and DSB decision are relevant to this analysis because of similarities in the type of technology, the motivations of the respondent, and the level of information available about risks at the time of the dispute. Genetically modified crops, while critically different from gene drive containing organisms, are the most closely related technology that was found in all prior WTO disputes. Central to EU systems to evaluate the risks posed by genetically modified crops was the precautionary principle

(Evans 2004), which may also motivate opposition to the release or spread of gene drive containing organisms. Compared to most issues contested SPS measures aim to address, less scientific information existed on how genetically modified crops may affect consumers. Even less information may exist on gene drive containing organisms by the time a WTO dispute would arise. That the EU rules were found to be inconsistent with the SPS Agreement indicates the stringent standard to which gene drive blocking measures would be held.

Analyses of this case have also pointed out the somewhat mysterious way in which the WTO incorporates scientific data into trade decisions. The DSB panel extensively questioned scientific experts in the course of its proceedings to weigh in on perceptions and assessments of risks of genetically modified crops. As Bonneuil and Levidow (2012) point out, more than 1000 pages, or over half, of its final report is dedicated to these discussions. Yet the panel's decision minimally addresses scientific arguments, characterizing its decision as legal, rather than scientific, in nature (Ibid.). How science was used to favor these complainants, and how it may be used to decide on gene drive cases, remains unclear.

Discussion

This research aimed to illustrate the range of scenarios in which trade disputes over gene drive containing organisms may occur, and to predict how trade disrupting measures in these scenarios may be interpreted by the WTO in the context of their SPS Agreement. Two sources of information were available for this assessment: the text of the SPS Agreement, and prior resolutions to disputes over SPS measures. From these, two contradictory conclusions can be drawn: the language of the SPS Agreement may well permit measures that block gene drive containing organisms, and measures that block trade are infrequently found justifiable. This contradiction, as well as the singularity of gene drive technology's nature and implications, and the lack of definitive knowledge of how gene drive containing organisms may impact species and ecosystems, makes prediction of how these disputes may be resolved difficult.

This analysis highlights key areas of uncertainty and potential contention around this technology. First, while the SPS Agreement appears to straightforwardly allow for measures blocking suppression drives, its governance of alteration drives may depend on less definitive connections between fitness cost and health. Alteration drives may affect the phenotypes and reproductive success of gene drive containing organisms in diverse ways; some could have no discernable effect while others could greatly reduce fitness and wellbeing. The interpretation of the impact alteration gene drives may have on health will likely need to be interpreted on a case by case basis, and expert opinion will likely be sought.

Second, countries that impose SPS measures to block gene drive containing organisms even though the altered species is not present in their country, out of concern for effects on non-target species, may or may not be found in violation of the SPS Agreement. Gene drive containing organisms could potentially alter ecosystems where the target species is not present. They could impact organisms they consume or are consumed by, or could alter landscapes. Additionally, gene drives could conceivably spread to closely related non-target species. For example, while Target Malaria is developing a gene drive system to alter *Anopheles gambiae*, which has a range confined to sub-Saharan Africa, other *Anopheles* species can be found worldwide. While there appears to be frequent genome shuffling within this genus, significant portions of genetic overlap can be found among the species (Neafsey et al. 2015). While interspecies mating is not known to occur, it is difficult to entirely rule out the possibility that offspring of gene drive containing organisms and individuals from other *Anopheles* species could be generated. It is possible that countries in which *Anopheles gambiae* is not present may oppose the entry of gene drive containing organisms for fear that the drive could spread to *Anopheles* species which are present through genetic drift. Whether such an SPS measure would be upheld may depend, among other things, on whether the genomic location of the drive was conserved among *Anopheles* or whether it was unique to *Anopheles gambiae*.

Finally, all known gene drive projects aim to alter wild, rather than agricultural, species, yet there is minimal precedent to understand how the SPS Agreement may be applied to cases involving the protection of wildlife. While measures aimed at protecting agricultural species may have similarities to those that would protect wild species, the assessment of risks is likely considerably more challenging in the latter case. Wild animals and plants cannot be studied to the same extent as their agricultural counterparts, and the systems in which they live are significantly more complex than farms and pastures. The standard to which countries imposing SPS measures to protect wildlife will be held in terms of demonstrated risk is yet unclear.

These uncertainties are unlikely to be clarified before a dispute occurs. The WTO is inherently reactive, rather than proactive, to new technologies. Most of its actions fall into one of its two primary activities: the creation of trade agreements, and the resolution of disputes when countries feel the agreements have been violated. When a new technology is developed, the WTO does not assess its impacts on trade or its applicability to trade agreements until a dispute is brought to its DSB. It does not advise countries or technology developers on trade impacts before disputes happen, and infrequently updates existing trade agreements to clarify the impact of a new technology. It is therefore unrealistic to expect clarity from the

WTO on the questions gene drive containing organisms pose for the SPS Agreement before countries are entrenched in a dispute.

While not analyzed here, international trade disputes over local gene drive systems are also conceivable. These disputes may center around confidence in the effectiveness of the localization technique employed. Neighboring countries might impose trade restrictions out of concern that the localization technique will not be sufficiently refined to prevent propagation across their border. Distant countries might, too, impose restrictions if they lack confidence that the localization strategy will persist over multiple generations as the species evolves. Conclusive demonstration of the success of localization techniques may be impossible before product release.

Avoiding disputes before they reach the WTO DSB is the most desirable outcome. Disputes generally take years to get resolved, during which time the participant countries may not be trading as they normally would. The economic, political, and social ramifications of such a disruption could be significant. GDP, inflation, and employment can be affected by trade disputes (Bachman 2018) and effects on political world order are even conceivable (Godbole 2018).

To avoid disputes, several groups should take action. International standard-setting organizations may be uniquely poised to address questions about managing this technology on an international scale. As stated in Article 3, the SPS Agreement requires members to harmonize their measures with international standards where they exist. Specially, Annex A lists the Codex Alimentarius Commission as authoritative on matters of food safety, the World Organization for Animal Health (formerly the International Office of Epizootics) as authoritative on matters of animal health and disease, and the International Plant Protection Convention as authoritative on matters of plant health. The expertise of these organizations is sufficiently valued at the WTO that the DSB generally does not entertain challenges to those standards, and instead views its role as determining only whether a respondent has violated an existing standard (Ni 2013). Notably, members of these organizations have argued that a broad interpretation of the SPS Agreement could empower them to set standards aimed at preserving biodiversity, in addition to their more traditional concerns of disease (Kahn and Pelgrim 2010), which may be of particular relevance to gene drive containing organisms.

Gene drive containing organism developers and the policymakers that oversee them are ultimately the most responsible for managing the impacts of this technology, trade and otherwise. These groups should consider localization and safeguard strategies that may make opposition to their product, as well as

international spread of the organisms, less likely. For instance, choosing genomic locations unique to the target species or population may reduce the number of countries whose species could be altered.

Development efforts, such as that being sponsored by the Defense Advanced Research Projects Agency (2017), to generate tools that can reverse gene drives, should be encouraged. Additionally, governments should converse with their trade partners while their technologies are being developed, to understand potential concerns and incorporate them into their development whenever possible.

Scientists must conduct additional research on the effects of gene drives, beyond their impact on target species. Understanding how gene drive containing organisms affect humans, other wildlife, and ecosystems will be critical for countries assessing their risks. These shortcomings of the existing understandings of gene drives were highlighted by the National Academies of Science, Engineering and Medicine in their report *Gene Drives on the Horizon* (2016). This in-depth analysis was funded by the National Institutes of Health to assess the escalating complexities of gene drive development. Further research that expands upon their findings should be supported.

Gene drive technology may offer unique opportunities to address serious issues for society. In the course of its pursuit, however, species and ecosystems may be affected, and human interactions could be disrupted. Trade is one of several areas that may be impacted by the release of gene drive containing organisms. To minimize their disruption, we must better characterize these tools, more effectively safeguard against potential harm, and more proactively communicate about our values and intentions.

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