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Regulating animals with gene drive systems: lessons from the regulatory assessment of a genetically engineered mosquito

Zahra Meghani[a] and Jennifer Kuzma[b]

[a]University of Rhode Island, Kingston, RI, USA; [b]North Carolina State University, Raleigh, NC, USA

ABSTRACT

For the purposes of conservation or suppression of species, gene drive technology has significant potential. Theoretically speaking, with the release of even relatively few animals with gene drive systems in an ecosystem, beneficial or harmful genes could be introduced into the entire wild-type population of that species. Given the profound impact that gene drives could have on species and ecosystems, their use is a highly contentious issue. Communities and groups have differing beliefs about nature and its conservation or preservation, as well as concerns about the ecological safety of the eradication, replacement or enhancement of particular species of animals by means of genetic engineering. For all those reasons, the rigorous regulation of insects and other animals with gene drive systems is crucial. In this paper, we consider the question of whether the United States Food and Drug Administration is prepared to effectively regulate insects and other animals with gene drives.

Introduction

The release of animals with gene drive systems in the wild could significantly affect ecosystems. The technology can be used to change, suppress and even eliminate particular species. Given considerable uncertainty and low levels of knowledge about the impact of the technology, the regulation of animals, including insects, with gene drives will be necessary. In the United States (US), the Food and Drug Administration (FDA) may well be responsible for regulating some animals with gene drives. Although it has not yet conducted risk assessment of animals with gene drives, in this article, we evaluate its preparedness to undertake that task. We also make suggestions for improving its risk assessment protocol so that it can conduct thorough risk evaluations of such animals.

Usually, an introduced gene is carried on one of a pair of chromosomes, and is thus inherited by about half of the offspring in the first generation (exhibiting Mendelian inheritance). Eventually, the gene becomes diluted in the natural population if it brings no selective advantage to the organism. With a gene drive system based on CRISPR/Cas9,[1] an edited gene on one chromosome can copy itself onto the partner chromosome

(Esvelt et al. 2014). The result is that nearly all offspring inherit the engineered gene. In organisms with short generation times and random mating, an engineered gene could be integrated across a large population within a season.

As of August 2017, animals with gene drive systems (with some exception)[2] are under the regulatory purview of the FDA. In 2016, the FDA approved field trials for Oxitec's genetically engineered (GE)[3] strain of the mosquito *Aedes aegypti* intended to the reduce population of its wild type.[4] In this article, we assess the preparedness of the FDA to regulate animals with gene drives *by scrutinizing its risk assessment of the Oxitec GE mosquito*. In doing so, we mirror the approach taken by the National Academy of Science, Engineering, and Medicine (NASEM). A 2016 NASEM report uses the World Health Organization (WHO) guidelines for 'regular' GE insects like Oxitec's OX513A GE mosquito to discuss risk assessment for animals with gene drive systems.

The FDA will regulate mosquitoes that are 'intended to reduce the virus/pathogen load within a mosquito, or products intended to prevent mosquito-borne disease in humans or animals' (FDA 2017). Furthermore, the regulatory system (including the laws and risk assessment requirements) initially used in 2016 for the OX153A mosquito is the same one that would be used to regulate most animals with gene drives (White House [2015] 2016). In addition, both the OX153A mosquito and possibly some animals with gene drives will be designed for the purposes of population suppression or elimination of their wild type. Thus, our analysis of the FDA's risk assessment of the Oxitec GE mosquito will usefully indicate FDA's readiness to rigorously evaluate mosquitos with gene drives. Also, it will identify ways in which the FDA's risk assessment protocol could be improved.

Given significant warranted concerns about mosquito transmission of diseases like malaria, Dengue and the Zika virus, mosquitos with gene drive systems may be the first animals with gene drives that are released in the 'wild.' Recent laboratory studies have demonstrated their potential effectiveness in replacing or eliminating mosquito populations (Gantz et al. 2015; Hammond et al. 2016). So, under the foresight goal of anticipatory governance (Barben et al. 2008), we use the OX513A mosquito case to anticipate and prepare for the oversight of gene drives in animals, particularly mosquitos.

In part one, we identify the normative concerns that influence the FDA's regulatory review. In part two, we analyze and evaluate the FDA's regulatory review of Oxitec's GE mosquito.[5] Specifically, we scrutinize the draft environmental assessment (EA) prepared by Oxitec and submitted to the FDA, and the agency's preliminary assessment of it (i.e. its Finding of No Significant Impact statement). We make the case that the agency's risk evaluation is not as rigorous as it could be. We also discuss the relevance of our analysis for risk evaluation of insects with gene drive systems. We close the paper by calling for the FDA to establish a transparent and democratic regulatory review process for new genetically engineered organisms (GEOs). This will enable it to more rigorously evaluate animals with gene drives and inspire warranted public confidence in its regulatory efforts and adhere to the 2016 NASEM recommendations about public engagement in decision-making about the use of animals with gene drives.

FDA's normative commitments[6]

In identifying and analyzing the FDA's normative commitments, we follow in the footsteps of other researchers. Jasanoff, for instance, has analyzed the role of political

culture in shaping the approach to risk assessment taken by different nations (2005, 21–22). Parthasarathy (2012) too has made the case that national context influences scientific and technological development, including systems of regulatory oversight. We extend their analyses by detailing the influence of neoliberalism on the US FDA's regulatory framework.

The FDA claims that its regulatory review of GEOs is solely science-based, and that it does not engage with normative questions. For instance, the FDA Center for Veterinarian Medicine has stated that it is not part of the agency's mission to engage with the public's ethical or economic concerns (FDA, CVM 2008, ii–iii; also see Meghani and Melo-Martín 2009). For example, the agency noted that the majority of public comments expressed opposition to GE animals for a multitude of reasons,

> including that manipulating the genomes of animals in ways that could alter their fundamental natures was, in and of itself, unethical or immoral, that experimenting with animals was wrong, that genetic engineering may have adverse social and economic consequences, that it is not possible to predict what such technology might lead to … (FDA 2008, Section K)

In response, the FDA claimed neutrality towards these issues when it responded to public comments on its draft guidance for industry about the regulation of GE animals (FDA 2008, Section K), asserting that those subjects were:

> … *largely outside the scope of FDA's authority*. The statutory and regulatory review and approval requirements for NADAs [i.e. new animal drug application] ensure that only drugs that are safe and effective are approved … The *moral, ethical, and socioeconomic issues outlined above do not fall within the scope of the guidance*. It is FDA's intent, however, that the regulatory approach described in *the guidance will provide a predictable science-based framework* that will ensure the safety and safe use of GE animals. (FDA 2008, Section K, italics added)

While the agency claims that it is not influenced by any ethical, political, religious or socio-economic considerations, normative considerations invariably shape risk evaluations (see, for instance, Meghani 2017a). Moreover, we contend that since the 1980s, the agency has been influenced by neoliberal considerations (see also Meghani 2017b).

The neoliberalization of the FDA

In 1938, the FDA was established by the Federal Food, Drug, and Cosmetic Act (FFDCA) (Barley 2007) as a reaction to the public health disaster caused by the drug company Massengill marketing diethylene glycol as treatment for streptococcal infections in children. The company had been selling the chemical without conducting any safety testing; its action resulted in numerous deaths (Barley 2007). The FDA was created to ensure that manufacturers of drugs and food did not cause harm to public health as they attempted to profit from their products. The agency aimed to provide the public with access to the safest food and pharmaceutical products and most efficacious medical products at the lowest possible cost to society.[7]

The implementation of neoliberal reforms has had substantial significance for the agency's regulatory function. According to neoliberalism, the state should have a minimal role in the economy so that the commercial sector can flourish, which, in turn, will benefit motivated, enterprising individuals (Harvey 2005). Many nations have

implemented neoliberal policies because they read them as serving their national interests. The US, for instance, justified its adoption of neoliberal policies on the grounds that they would benefit American companies, and thus, US interests (see Meghani 2017b).

The neoliberalization of the FDA began in the 1980s with the Reagan administration issuing Executive Order #12291, which scrutinized existing and new regulations to evaluate their economic impact (Federal Register 1981). The aim of the Order was to cut down or entirely dispense with federal government regulations, with the end of allowing the private sector to govern itself because (the administration believed) it would stimulate economic growth, raise productivity and reduce the cost of doing business (Reagan 1982).

A year earlier, in 1981, George A. Keyworth (President Reagan's Chief Science Advisor) had given testimony before the House of Representatives' Committee on Science and Technology, emphasizing that enterprising individuals and the private sector should take the lead in science and technology, with the federal government reducing its role. The FDA was targeted by the Reagan administration for neoliberalization because it was 'quite good at confronting businesses and reigning in their profit-seeking behavior if their interests conflicted with the public interest' (Markel 2005, 2490). But a key problem with neoliberal theory is that it fails to acknowledge that the industry's interests (of maximizing profits) can be at odds with the public interest, in this case, protecting public health and the environment.

Neoliberalization of the regulation of biotechnology

The neoliberalization of the US biotechnology regulatory framework and FDA's policies for food biotechnology have their roots in the 1986 *Coordinated Framework on the Regulation of Biotechnology* (CFRB) (Meghani 2017b). Issued by the White House's Office of Science and Technology Policy (OSTP), the policy framework was the nation's first key regulatory document about GEOs. The CFRB asserted that GE food should be treated the same as their non-GE counterparts and therefore no new laws were needed to regulate GE food and the products of biotechnology. This policy stance was justified on the grounds that it would allow the US to lead and dominate the global development of and trade in biotechnology (Federal Register 1984; Levidow, Murphy, and Carr 2007, 34).

In 1992, the FDA published a guidance document for industry outlining a process by which biotechnology companies could voluntarily consult with the agency about new plant varieties developed using genetic engineering (FDA 1992). This *Guidance* formally established the kind of close relationship between the state (in this case, a regulatory agency) and industry that neoliberalism advocates.[8] FDA reviewers were formally instructed to no longer to be at arm's length from the developers (or sponsors) of new biotechnologies. An aim of the agency now became to help sponsors of new food products get approval so that they could bring GE products to market as soon as possible (Hilts 2003, 228). For example, in the 1992 *Guidance*, the FDA identified itself as concerned with the best interests of the GE food industry (which it aligned with its own interest):

> *FDA believes that it is in the best interests of the regulated industry and the agency for developers to inform FDA*, as discussed below, prior to commercial distribution, about foods or feed derived from new plant varieties, including those derived using rDNA techniques … (FDA 1992)

In 2017, 31 years after the original CFRB was issued, the US issued a revised CFRB. As a precursor to the 2017 CFRB, in 2015, the White House issued a 'Memorandum on Modernizing the Regulatory System for Biotechnology Products' (White House [2015] 2016). The memo revealed the state's continued commitment to a neoliberal worldview. It initiated a process to 'clarify' the 1986 CFRB to 'ensure public confidence in the regulatory system and to prevent unnecessary barriers to future innovation and competitiveness by improving the transparency, coordination, predictability and efficiency of the regulation of biotechnology products while continuing to protect health and the environment.'[9] This statement expressed a commitment to fostering innovation and trade competitiveness (and, thus, corporate biotechnology interests) that seems to go beyond regulations that protect human health and the environment. In fact, it appears to treat fostering innovation and global market competitiveness (and thus, industry interests) as having the same importance as protecting and advancing public health.

In the case of gene drive technology, the model for innovation is likely to include non-profit organizations interested in community health or conservation (e.g. Target Malaria project) (see also Kuzma et al. 2017), in addition to for-profit companies. The push for innovation and market entry would favor the development of GE mosquitos, whether their sponsors are non-profit organizations or for-profit entities. Next, we analyze the FDA's risk assessment of the Oxitec mosquito. We believe that the agency's evaluation is not as rigorous as it could and should be.

FDA's review of Oxitec's (draft) EA

In this section, we delineate the policy framework for the FDA's regulatory authority over GE animals. Then we analyze and evaluate the (draft) environmental risk assessment for the GE mosquito (OX513A) submitted to the FDA by Oxitec as part of its application to the agency and the FDA's (preliminary) evaluation of that report (i.e. FONSI) in making its decision about whether to approve field trials of the OX513A mosquito. We make the case that the FDA's (draft) Finding of No Significant Impact (FONSI) is not justified given the data that was provided to the agency by Oxitec.

The FDA has claimed regulatory authority over certain GE animals (including insects that are not plant pests) by evoking the FFDCA, the CFRB and the FDA's own *Guidance* (2009). The 2009 *Guidance* delineates the agency's regulatory policy for GE animals, including insects. The *Guidance* (2009) treats GE animals as 'new animal drugs' (NADs) because the intentionally altered genomic DNA introduced in the animals is meant to impact their bodily structure or function. The FFDCA construes as a drug all non-food articles that are meant 'to affect the structure or any function of the body of man or other animals' (21 U.S. Code 321, section 201(g)). Developers of GE animals must submit a new animal drug application (NADA) to the FDA's Center for Veterinary Medicine (CVM). The NADA applies to the intentionally altered genomic DNA in the animal. Thus, the agency regulates the article in the GE animal, not the GE animal as a whole (FDA-CVM 2009; revised 2015 & 2017, 6), despite using language suggesting regulation of the animal as a whole (FDA-CVM 2009, 7; see also Meghani 2017b). *Under the current FDA regulatory system, animals with gene drives would be classified as NADs.*

The FDA's decision to regulate GE animals under the FFDCA NAD provisions has ethical and political consequences. For example, the NAD process allows developers of

GE animals to claim that crucial details about the biotechnology are trade secrets, shielding them from public scrutiny. Specific to animal drugs and the NAD provisions 21 C.F.R. § 514.11b, the FDA is barred from making public that it is reviewing an NADA until the NAD approval has come out in the *Federal Register* (unless it has been disclosed or acknowledged by the sponsor of the drug (Otts 2014)). For instance, because the Aqua-Bounty GE salmon and the Oxitec GE mosquito were classified as NADs by the FDA, the biotechnology companies did not have to disclose to the public that they had submitted an Investigational NAD (INAD) application to the FDA. However, the developers of the two GE animals voluntarily made it public that their products were under review at the FDA; they shared the risk assessments with the public in the draft comment phase of the regulatory review process. Our larger point is that the state (including the FDA) serves industry interests by making it legal for corporations to not disclose to the public that they have submitted an application for a new drug for regulatory approval. If GE animals were regulated by other agencies, such as Fish and Wildlife Service (FWS) under the Endangered Species Act or the Lacey Act, the public could have greater access to information about them as the information would not be subject to the more stringent protections under the FDA's NAD provisions. Instead, the agencies would be able to notify the public that products are under review and share draft documents and assessments during the review, as the Freedom of Information Act generally requires federal agencies to disclose information (Unlu 2009). For example, on its website, the USDA puts out notice of the ongoing review of GE plants when a petition for deregulation is filed and before a decision is made (USDA 2017).

Gene drives in insects and other animals are likely to be subsumed under the same provisions and regulatory processes as the OX153A mosquito. Therefore, in the interest of anticipating and preparing for gene drive governance, it is instructive to look at the regulatory review and risk analysis process for the OX153A mosquito and consider ways for improving them. Both the OX153A mosquito and insects with gene drives designed for population suppression will contain engineered genes that do not allow the offspring to survive and are designed to spread to reach the wild population in the target areas. The assumption is that the GE mosquitos will mate with the wild population, resulting in the decrease in its numbers. The potential categories of ecological risks associated with the spread of both types of engineered mosquito populations are also similar (see NASEM 2017, and more on this later), although the time and geographic scales may differ.

But it must be acknowledged that there are differences between the Oxitec mosquito and gene drive mosquitos. For example, in the case of the OX153A mosquito, continuous releases of large batches of engineered mosquitos will be needed to eliminate the wild population. With a gene drive mosquito, fewer releases and smaller numbers of insects are likely to be required to wipe out an entire population (assuming close to 100% inheritance of gene drives with each generation, versus 50% inheritance of the OX513A killing gene with each generation) (Burt 2003). It is beyond the scope of this project to compare how an actual *risk assessment* for the two (the OX153A mosquito versus a mosquito with a gene drive) would differ at each stage of the process, as natural scientists and risk assessors are still debating these issues (NASEM 2016).[10]

This paper argues that the risk analysis process for GE animals under the NAD provisions is flawed in its interpretation of the data and uncertainties. While this complicates managing risk for both the OX153A mosquito and gene drives (see below), the problems

may be exacerbated with gene drives because of their (anticipated) greater effectiveness in spreading genes in wild populations. With the OX153A technology, if the mosquitos releases are discontinued (e.g. because of a report of an unanticipated ecological event), it is more likely that the wild population would recover than in the case where gene drives are used.

The Oxitec mosquito: assessment under the National Environmental Policy Act

The GE mosquito (OX153A) is designed to suppress wild populations of *A. aegypti* in regions with Dengue fever and the Zika virus, with the aim of decreasing viral transmission to humans (FDA-CVM 2016). The OX153A GE mosquito passes a lethal gene to its offspring, which, in the absence of tetracycline,[11] causes them to die (Harris et al. 2012). While the OX153A mosquito strain of the *A. aegypti* mosquito does not contain a gene drive that propagates through super-Mendelian inheritance, it results in an effect similar to mosquitos with gene drives designed to suppress mosquito populations for human disease control (Burt 2003; Esvelt et al. 2014). Thus, in a sense, it is a precursor to insects engineered with population-suppressing gene drives. The result is the same – to decrease the presence of a pest using a GE animal.

The FDA must comply with the National Environmental Policy Act (NEPA) as it considers field trials for GE animals, including the Oxitec GE mosquito (under the NADA and the FDA's 2009 *Guidance* (for GE animals)). The FDA construes field trials as analogous to clinical trials of NADs. The FDA reviewed the OX153A mosquito under the INAD provisions of the FDCA, and in summer 2016, published its final assessment documents (consisting of Oxitec's EA report for the GE mosquito and the agency's own FONSI statement), approving field trials. The Oxitec mosquito was slated for release in the US Florida Keys, where cases of Dengue had been documented and there was concern about Zika.[12] The OX153A mosquito has thus far been released in Brazil, Malaysia, the Cayman Islands and Panama. In those locations, it has been shown to reduce the target wild-type mosquito population in field trials (Nimmo and Beech 2016). However, from our analysis of Oxitec's (draft) EA report and the FDA's (preliminary) FONSI, it appears that Oxitec has not provided the FDA with any data on the ecological monitoring of non-target organisms or other environmental endpoints related to those releases.

NEPA requires that federal agencies follow established environmental review procedures, which include evaluating and documenting the environmental impact of any significant federal action. Regulations under NEPA (40 CFR 1500–1508) establish three levels of environmental review with progressively greater detail and rigor: categorical exclusions, EA and environmental impact statements (EIS). The EIS is the most robust EA; in contrast, classification as 'categorical exclusion' means that no environmental evaluation is required. While the FDA has to abide by NEPA (as mentioned above), the agency's regulatory decisions about GE animals are based on its authority under the FFDCA, the NAD provisions and the 2009 *Guidance* (on GE animals). Under the FFDCA, the FDA evaluates the safety of the drug for the animal on which it will be used, and it assesses the efficacy of the drug (i.e. does it do what it claims to do?). The product developer submits an INAD for clinical trials (in the case of Oxitec's GE mosquito, field trials function as clinical trials), and then after the trials are conducted, the developer submits a NAD application for interstate commerce. The FDA uses NEPA to better address broader environmental concerns

and motivate product developers to attend to those concerns in their own risk management plans.

Compliance with NEPA has been a point of contention in the regulation of GEOs generally. Lawsuits have been brought against the USDA by consumer and environmental groups on the grounds that the agency did not adequately assess environmental endpoints (as required by NEPA) for GE plants because it did not choose its most rigorous option, i.e. the drafting of EIS (reviewed in Cowan and Alexander 2012). Several consumer and environmental groups are suing the FDA for its recent approval of the GE AquaBounty Salmon, and one reason for the lawsuit is the lack of an EIS (see, for instance, Keat et al. v. U.S. DHHS FDA 2016).

For the OX513A GE mosquito, the FDA made the decision that an EA was sufficient and therefore allowed Oxitec to submit a (draft) EA report as part of its INAD application. After reviewing Oxitec's application, the agency issued a (preliminary (i.e. draft)) FONSI document. This choice has ethical and political import given the uncertainty and novelty of the GE 'product' and its purpose. Notably, mosquitos are mobile organisms, and the intended aim for GE mosquitos is for them to mate with their wild-type counterpart, decreasing their population size. Our point is that the aim of strict containment of the GE mosquito in a 'clinical trial' (or field trial in this case) is at odds with the motivation underlying the release of the OX153A mosquito. Careful attention to assessing ecological impacts *prior* to release is important for this GE insect, and for all GE animals with gene drives.

The conundrum in the case of GE animals designed to spread and mate with wild populations is that in order to test the efficacy of this new animal 'drug' in a field trial (in this case, manifested by wild type *A. aegypti* population suppression), the organism needs to spread to wild populations of its species. This also means that the GE animal will come into contact with non-target species as they spread. Unanticipated consequences of the release of the GE insect during the so-called field trials (i.e. INAD period) thus constitute a serious concern. The FDA's decision to accept this uncertainty by allowing for the open release of the OX513A mosquito, without rigorous prior analysis to support its safety (e.g. in an EIS), is worrisome. It brings into focus the tension between its obligation to protect public health and duty imposed on it to foster biotechnological innovation. The agency's decision carries ethical and political significance. It would have been better if the agency had prepared the (rigorous) EIS, and considered in detail the potential ecological impacts, societal ramifications and tradeoffs compared to alternatives. It is also worth considering that by opting to give environmental concerns less attention by preparing an EA report rather than an EIS, the FDA is opening itself up to additional lawsuits from non-governmental organizations concerned about GE animals and their ecological impacts. Moreover, the agency's evaluation of the (draft) assessment documents for the OX153A mosquito (FDA 2016; Oxitec 2016) makes several unwarranted assumptions. But we do not read these shortcomings as a sign of epistemic incompetence of FDA risk assessors. Rather, we interpret them as evidence of the agency's attempt to foster the biotechnology industry's interests, even as it seeks to attend to its mission of protecting public health.

The Oxitec mosquito: FDA's decision to review a GE insect as a NAD

The OX513A mosquito strain has been engineered to include genes that in the absence of tetracycline will kill the organism in the larval stage. Because female mosquitos are the

ones that bite, Oxitec aims to release only GE male mosquitos. But with an approximate 99.9% efficiency rate, 0.1% or about one out of a thousand GE female mosquitos will be inadvertently released (Oxitec 2016). The strain also has a marker gene from marine coral, DSRed2, that allows for detection of mosquitos containing the engineered genes, as well as other DNA sequences from Cabbage moth, Drosophila and *E. coli* that regulate the genes and help insert it into the host's genome.

Oxitec's INAD trial is designed

> to evaluate the mating ability of the OX153A male mosquitoes with local wild type non-GE *Aedes aegypti* females, to assess the survival to functional adulthood of the resulting progeny inheriting the #OX513 rDNA construct as compared to local non-GE progeny, and to estimate the efficacy of sustained releases of OX513A male mosquitoes for the suppression of the local population of *A. aegypti* in the described release area in the Florida Keys. (Oxitec 2016, 37)

Thus, the field trial for which Oxitec is seeking approval (from the FDA) is designed to evaluate, first, the drug (i.e. rDNA construct) safety with respect to the animal, which is the lab-raised GE mosquito (the gene is designed to kill the progeny in the wild),[13] and second, drug effectiveness (how well does the GE mosquito or its rDNA construct reduce the target *A. aegypti* mosquito population). There is no mention in Oxitec's description of the field trial of assessing and collecting data on the potential, unanticipated impacts on local ecosystems (including non-target organisms), horizontal gene flow, effects on prey of the mosquito and many other relevant factors (i.e. endpoints) (Oxitec 2016, 37–38).[14] This omission has normative significance because it limits the scope of the regulatory assessments to very few outcomes and omits various other relevant impacts.

Presumably, the FDA is aware that the goals of Oxitec's proposed field trial are very limited, but it has not urged the biotechnology company to study other relevant outcomes. The FDA's FONSI appears to unquestioningly accept the agenda set by the biotechnology company:

> The goals of the proposed investigational trial are to evaluate the breeding of the OX513A mosquitoes with local wild-type *Aedes aegypti* females, to assess the survival of the resultant progeny, and to estimate the suppression of the overall *Aedes aegypti* population at the trial site relative to an untreated comparator area. (FDA 2016, 2)

Thus, the FDA regulatory process for the GE mosquito is primarily concerned with determining the efficacy of the 'drug.'

GE animals with gene drives will probably be under the same FDA regulations as the OX153A mosquito. As argued above, the FDA has claimed authority over certain GE animals by classifying them as NADs. This categorization means that field trials of new GE animals are likely to be limited to assessment of the introduced gene's effectiveness as a drug or safety for the animal in which it is introduced. At this point in time, we have found no evidence that the regulatory review of animals with gene drives under FDA will be subject to more comprehensive ecological assessment than in the case of the OX513A mosquito. We worry the limited focus means that during the review process the effects of the introduction of animals with gene drives on non-target organisms, biodiversity and indirect impacts on human health and the socioeconomic circumstances of various groups may not receive sufficient attention.

Assumptions about GE mosquito survival probability and possibility of spread in the wild

Oxitec's EA statement indicates that up to 5% of the GE mosquito population with OX513 tTAV genes may survive in the absence of tetracycline (Oxitec 2016, 52). If 5% of the second generation progeny survive (with approximately half of that population being female), then this means survival of female-biters with the OX513A gene and potential egg-layers to sustain the GE trait in third generations and beyond. Reeves et al. (2012) also state that 'OX513A males are only partially sterile, and when they mate with wild females, they will produce 2.8–4.2% surviving larvae of eggs, half of which will be biting daughters.'

Tetracycline is present in the environment in wastewater and agricultural systems because it is used for animal agriculture and human health (Oxitec 2016). Accumulations of tetracycline antibiotics have been found in living systems and in surface, ground and waste water (Daghrir and Drogui 2013). There could be bodies of water where the concentrations of tetracycline are high enough such that the lethality gene will be repressed in the OX513A mosquitos that have access to that water. Near the proposed release site in the Florida Keys, there are two wastewater treatment sites, which could increase concentrations of tetracycline in standing pools (Oxitec 2016, 53). Worldwide studies have reported tetracycline levels in the environment at concentration levels that increase survivability of larvae: 1–3 ng/L survivability doubles number of GE mosquito larva that emerge from about 4–8%, and general environmental concentrations have been reported at 1.4 ng/L with some reaching the microgram per liter range near wastewater or hospital sites (Oxitec 2016, 53). Oxitec assumes (without testing standing water in the Florida Keys) that sunlight will degrade the tetracycline down to no-effect level concentrations near the wastewater sites and that the only concentration that matters is the one that increases mosquito emergence from 4% to over 60% in the microgram per liter range (µg/L) (Oxitec 2016, 53).

It would have been reasonable for the company to have tested standing water near homes in the Florida Keys, and used the data in a risk analysis to determine what levels of tetracycline exist in the area of release and what proportion of larva are likely to emerge at those environmentally relevant concentrations. The EA also did not take into consideration the relevance of tetracycline concentrations that cause between 4% and 60% mosquito emergence (i.e. between 1 ng/L and 1 µg/L) even though it is plausible that those levels of the chemical could be found at the proposed field trial site. In any case, given that about 4% of second generation larvae will survive even in the absence of tetracycline, and more GE mosquitos will survive in concentrations of tetracycline in the environment above 1 ng/L (the level routinely found in the environment), there is likely to be a higher proportion of females with the OX513A gene in the environment than acknowledged in Oxitec's EA or the FDA's FONSI statements. However, the agency did not require of Oxitec that it address these significant omissions in its EA. That raises troubling questions about the agency's efforts to meet its obligation to protect public health and foster biotechnological innovation.

Oxitec indicates that the field trial will involve the release of GE mosquitos up to three times a week for up to 22 months (Oxitec 2016, 38). With every release, about 0.1% GE females are released (the separation efficiency of the GE mosquitos by sex in the laboratory

is about 99.9% effective). These three sources of leakage in the system – released GE females, imperfect operation of the molecular repressor system and presence of tetracycline in the environment – mean that GE mosquitos may persist in the environment, even if their percentage may be relatively small in contrast to their wild-type counterparts. This possibility is not quantified, and survivability of the GE insect over time is not modeled under the field trial conditions in the EA document, leaving the question of persistence unanswered.

Moreover, the EA report that Oxitec submitted to the FDA does not attempt to model the proportion of GE to non-GE mosquitos over time, nor does it present an uncertainty analysis to calculate the distribution of possible prevalence of GE mosquitos and the likelihood at each prevalence. The agency decision to not require of the company that it perform quantitative risk or exposure assessment with uncertainty (in order to factor in variation over sustained multiple releases) is worrisome. It appears to unjustifiably discount the concerns that some groups may have expressed about the persistence of the GE organism in the environment even after the field trial is over.

The FDA also makes the following (arguably unwarranted) claim in its FONSI document about the duration of the trial and spread:

> Risk of establishment or spread has been determined to be negligible. The investigational trial is short in duration and any unanticipated adverse effects are unlikely to be widespread or persistent in the environment. (FDA 2016)

It is a matter of perspective whether releases for 2 years, up to three times a week (300 releases) 'with sustained releases that are adapted to the numbers of the *A. aegypti* in the environment' (Oxitec 2016, 37), reflect a trial 'short in duration.' Given the information provided in the EA, it is also not certain that long-term or widespread impacts are unlikely.

The FDA FONSI denies the possibility that some GE mosquitos will persist, despite the evidence of leakiness in the molecular system (as discussed above, about 4%). The agency asserts,

> At the conclusion of the investigational field trial, the OX513A mosquitoes would die off at the end of their natural lifetimes in the environment (approximately two days) and wild-type *A. aegypti* levels are expected to recover to pre-trial numbers. (FDA 2016, 5)

It is arguable whether the agency is justified in making such a strong claim; the detailed information provided in Oxitec's (draft) EA statement on leakage in the system and the survival probabilities of GE mosquitos do not appear to warrant the agency's conclusion. The probability of survival of the GE mosquito is low, but it is not zero. The GE mosquito can survive more than 2 days, especially when tetracycline is present in the environment (Oxitec 2016, Appendix F, 5). In fact, a high percent (40%) survive more than 2 days in the absence of tetracycline, with 20% surviving more than 15–20 days (Appendix F, Oxitec 2016). The conclusion, however, strongly suggests that the FONSI interpretation of the Oxitec data is not rigorous. The FDA's statements appears to support the environmental release of mosquito (to the benefit of Oxitec), even in the face of considerable uncertainty.

If survival of the GE mosquito is a serious possibility, what about the probability of their dispersal in the environment? The Oxitec EA states that because *A. aegypti* live primarily in human-managed ecosystems (e.g. tires filled with water outside homes), non-target

exposure outside of these areas is limited. However, the (draft) EA statement also mentions field collection surveys that found that the species can indeed be found in protected national wildlife areas where endangered animals live, albeit at low frequencies (Oxitec 2016, 44). Instead of requiring Oxitec to account for these (partially) contradictory statements, the FDA's draft FONSI accepted the declaration about the mosquito's inability to thrive outside of human-managed areas.

The agency's assessment of spread of the GE mosquito in the environment also raises questions. Some GE mosquitos can indeed survive in subsequent generations and live more than a few days (as indicated by the graphs on page 6 of Appendix F); thus, some GE mosquitos could possibly travel over multiple generations to wildlife areas where non-target impacts could be of greater concern than in the area of the original release. Yet, the FDA claims that 'it is extremely unlikely that OX513A mosquitoes would disperse beyond the trial area' (FDA 2016, 5). Some studies show that some females can indeed fly well over 200 m (Oxitec 2016, 66). Moreover, Oxitec's review of the scientific literature indicates that passive transport (on ships, trains, cars, etc.) is the primary means by which the mosquito has spread in Florida, and has even reached California (Oxitec 2016, 66; Gloria-Soria et al. 2014).

FDA also claims in its concise (6 page) FONSI that:

> [t]he population of *A. aegypti* at the proposed site is expected to return to its original levels upon completion of the proposed investigational trial due to migration of wild type *A. aegypti* from areas that did not receive OX513A male mosquitoes. (FDA 2016)

That seems to imply that the *A. aegypti* mosquitos will necessarily travel in that direction to (re-)establish a habitat, but that assumption is unwarranted.

The decision to not perform quantitative risk assessment, collect data in the field trial to enable an assessment, or use outside experts in 'weight of evidence' or Bayesian expert elicitation approaches are a value-laden choices. There is sufficient data available to model the prevalence of the mosquitos over time with uncertainty reflected in distributions of possible values. The EA could have calculated the number of females and males mosquitos released, the survival of larva in the second generation due to the leakiness of the molecular construct and presence of tetracycline, and the spread over geographic areas. Oxitec and the FDA employ language that is vague and seems to downplay the non-zero probability of survival and spread because they did not perform a quantitative assessment as part of the EA. If a quantitative assessment had been conducted, the transparency of the evaluation would have been greater (e.g. '10–1000 females surviving in a 5-mile range' makes the exposure to the mosquito 'highly unlikely').

In the EA statement, Oxitec chose to use a qualitative risk assessment method that combines phrases of 'likelihood' with phrases of 'consequence' to estimate 'risk' qualitatively (Oxitec 2016, 102). The EA statement includes a table with various pathways and endpoints for different potential risks. Most of these risk pathways have a likelihood of 'highly unlikely' and a consequence of 'minor' or 'marginal,' thus putting Oxitec's overall estimation of risk for these various harms considered in the table at 'negligible.' In contrast to the approach used by Oxitec, the FDA's FONSI uses different and somewhat contradictory language to characterize the risk. The agency states that '[b]ecause risk is a function of hazard and exposure, if exposures are negligible, risk will also be negligible' (FDA 2016). However, in the Oxitec EA's risk assessment framework, exposures are not

categorized using the term 'negligible'; the biotechnology company characterizes the exposures as ranging from 'highly likely' to 'highly unlikely.' The FDA's statement is also at odds with risk assessment scholarship. For example, low levels of a very toxic compound, such as ricin, can lead to greater severity of illness and thus greater risk upon lower exposures when compared to compounds that are less toxic. Also, fault tree analysis for low probability yet high-consequence events (like a nuclear power accident) is a standard approach in risk analysis. A low probability of events (or exposures) can lead to high risk if the impacts are severe. For example, an Australian risk assessment group chose to model a GM mosquito (with the bacterium Wolbachia) and population suppression risk with a fault tree, which considered multiple pathways of failure and endpoints for human and ecological health, social impacts and economic effects (Murphy et al. 2010). This method of risk assessment would have been more appropriate for the Oxitec GE mosquito than the one employed by Oxitec and the FDA.

Uncertainty is also evaluated qualitatively in the Oxitec EA statement. For example, the EA states,

> The potential likelihood (of the OX513A mosquito) … establish[ing] in the environment has a medium confidence of uncertainty, because it would require detailed information on each environmental variable that could affect establishment, such as temperature, humidity, larval competition, predation, breeding site, container, vegetation etc. Even if such information were available, the interactions of the environmental factors and the organism itself would still provide a degree of uncertainty in the analysis. (Oxitec 2016, 118)

Yet, Oxitec then states (in the same paragraph) that there is a 'high degree of certainty that the OX513A is unlikely to establish in the environment' (Oxitec 2016, 118). To state the obvious, it is contradictory for the EA to simultaneously claim that the potential for establishment is of 'moderate uncertainty' *and* 'high degree of certainty.' Instead of imprecise and conflicting qualitative descriptions of uncertainty, the FDA and Oxitec assessments could have portrayed the uncertainty and variability for each parameter through the use of probability distributions, or used expert judgement to derive these distributions through fault or event tree models (see, for instance, Murphy et al. 2010).

In rendering its decision in the FONSI, the FDA does not address the (above mentioned) lack of data as well as the overall uncertainty (FDA 2016):

> The consequences of escape, survival, and establishment of the OX153A mosquito in the environment have been extensively studied: data and information from those studies indicate that there are unlikely to be any adverse effects on non-target species, including humans. Risk of establishment or spread has been determined to be negligible. The investigational trial is short in duration and any unanticipated adverse effects are unlikely to be widespread or persistent in the environment. Most importantly, the status of the environment is restored when releases are stopped (i.e. the released mosquitoes all die, and the environment reverts to the pre-trial status). FDA has therefore made the preliminary finding that the proposed field trial would not individually or cumulatively have a significant effect on the quality of the human environment in the United States, and is issuing this preliminary FONSI.

As of now, there is no field trial data for escape, survival or establishment in Florida; only limited field trial data on efficacy are available for other locations where Oxitec has released the OX513A mosquito strain. Field trials in the Cayman Islands and Brazil

have shown a temporary reduction in *A. agypti* populations in the trial site (Harris et al. 2011; Carvalho et al. 2015). As yet there are no published scientific reports that the GE mosquito will reduce the disease in human populations (Boëte and Reeves 2016). Second, according to the information provided by Oxitec to the public, the company has not monitored non-target impacts, population replacement and human health impacts in past releases (of the GE mosquito) in other countries. Furthermore, while the risk of OX513A establishment in the environment was determined by Oxitec to have 'moderate uncertainty,' much more data would be required to 'reduce' that uncertainty. Third, not everyone would consider 2 years of mosquito release up to three times per week a 'short' trial period. Fourth, the released mosquitos will not all die within a 2-day period, and there is some uncertainty about whether GE mosquitos will establish in the target area or spread to other locations. To sum up, multiple value judgements are embedded within Oxitec EA statement and FDA's FONSI document. The FDA's acceptance of qualitative interpretations from Oxitec's risk assessment seems to raise questions about the agency's efforts to meet its obligation to foster biotechnological innovation even as it seeks to protect public health and the environment.

An alternative way forward

Given the shortcomings of the (draft) risk assessment and (preliminary) FONSI for the GE mosquito, we recommend that the FDA makes significant changes in its risk evaluation protocol as it attempts to regulate other GE animals. This is especially important for the case of self-sustaining gene drives where the assessment of risks prior to field trials is crucial given the potential that the genetic modification could affect the entire species in an ecosystem or the larger series of interconnected ecosystems.

The agency should begin by acknowledging that its risk assessments are shaped by normative considerations, and it should require of the developers and sponsors of new biotechnologies that they do the same. To reiterate, any and all values influencing risk assessments (such as the FDA's commitment to fostering the biotechnology sector and the desire of the sponsor of the GE animal to have their 'product' reach the marketplace as soon as possible) must be acknowledged. It will also be crucial that they identify the 'junctures' in the risk evaluation process where those values are at work (Kuzma and Besley 2008), so they can be publicly interrogated.

The transparency will mean at least three things. First, the agency will either not be able to refuse to engage the normative concerns of the public on the grounds that it is inapplicable to its work or it will have to justify why public's normative concerns are not applicable when the normative concerns of the agency and developers are relevant. Second, the agency and biotechnology sponsors will not be able to employ (traditional) scientific conceptions of risk and safety to dismiss those worries as lacking scientific merit and thus any significance (Thompson 1997). And third, the normative concerns that shape any risk assessment will be available for public deliberations. Such risk assessments will be less likely (compared with risk evaluations generated under the current risk assessment protocol) to foster the biotechnology industry's interests without the public's scrutiny and consent. That will do much to inspire warranted public confidence in the agency regulatory efforts, and ensure that it abides by the NASEM's recommendations about public engagement in decision-making about gene drives (NASEM 2016). Our larger point is

that transparency will open the door to the engagement of multiple experts, stakeholders and publics in a more democratic risk assessment process, which will control for unacknowledged and unchallenged biases, resulting in more rigorous risk assessments than the current ones. In other words, transparency will bear ethical, political and epistemic (read: scientific) fruits.

The (above) fundamental and broad shifts in the risk assessment protocol must be accompanied by specific changes. Some of the ways in which the rigor of the risk assessment could be bolstered include additional justification for the interpretation of presented data, opening up the risk assessment process to outside experts, use of probability distributions to characterize uncertainty and incorporation of models to consider low probability events (such as fault trees). In the case of gene drives, the collection of additional data on non-target impacts in laboratory or mesocosm studies is also warranted (Oye et al. 2014). These changes will be of particular importance for animals with gene drives, given their ability to suppress or cause changes in species within multiple ecosystems.

Conclusion

Given the 2009 *Guidance* and recent updates to the CFRB (FDA 2009, revised 2015 & 2017; White House [2015] 2016), some animals with gene drives[15] may to be categorized under the NAD provisions and the same regulatory processes as the 2016 classification of the OX153A mosquito. There are similarities in the risk endpoints of concern between animals (including non-mosquito insects) with gene drives designed for population suppression *and* the OX153A mosquito (e.g. consequences of decline of a population and impacts on predator–prey relationships). Furthermore, ecological risks associated with the spread of GE animals and animals engineered with gene drives fall in (similar) general categories (e.g. harm to non-target species from consumption, horizontal gene flow and impacts, etc.), although the pathways to those risks may change, as well as the temporal and geographic dimensions (see NASEM 2017).

In this paper, we used an example of existing regulatory practices to identify key problematic assumptions in an FDA's risk assessment. On the basis of that analysis, we have offered recommendations for improving the FDA's risk analysis process for animals with gene drives. We urge their adoption by the agency before it is faced with the challenge of regulating such entities. Particular care is called for in initiating field trials for animals with gene drives.

For the sake of fulfilling its mission to protect the environment and public health, to increase the reliability and credibility of its regulatory review, and to invite warranted public confidence in its regulatory activities (whilst avoiding even the semblance of bias towards the biotechnology industry), the FDA should re-shape its regulatory process to allow for broader study of possible ecological impacts, including impacts on humans. It should also give public constituencies the opportunity to participate in a substantive sense by deciding which values should shape the risk assessment of GEOs (see, for instance, NRC 1996 or Meghani and Kuzma 2011; Meghani 2014). Given the ability of gene drives (especially self-sustaining ones) to permanently alter or eradicate populations in the wild within an ecosystem or across ecosystems, it is crucial that the public(s) in the US and other nations jointly have this opportunity.

Notes

1. CRISPR denotes Clustered Regularly Interspaced Short Palindromic Repeats. Cas9 is a nuclease that makes cuts in DNA next to CRISPR sequences. These have been engineered and harnessed for gene editing.
2. Plants pests are to be regulated by the United States Department of Agriculture (USDA).
3. We use 'GE' in this paper to indicate organisms manipulated in the laboratory by modern biotechnology methods such as recombinant DNA technology and gene editing. Note that 'genetically modified' (GM) is used often in countries outside of the US.
4. The Oxitec mosquito that is the subject of this paper is currently under the regulatory authority of the EPA. The FDA had originally laid claim to regulatory power over the GE mosquito on the grounds that the rDNA construct introduced into the mosquito qualified as a drug. In February 2016, Oxitec submitted the draft EA that it had prepared to the agency. A month later, the agency issued a preliminary FONSI statement. (This paper was written in the wake of the issuance of the draft EA and FONSI.) After soliciting public comments on the draft Environmental Assessment and preliminary (FDA) FONSI, in August 2016, the FDA posted on its website its (final) Environmental Assessment and FONSI. Then, in October 2017, the FDA issued the guidance document, 'Clarification of FDA and EPA Jurisdiction Over Mosquito-Related Products.' In it, the agency ceded authority over GE mosquitos, including the Oxitec mosquitos, which have a pesticide function to the EPA. This change of regulatory jurisdiction for the GE mosquito was justified on the grounds that in 1975 Congress had amended the Federal Insecticide, Fungicide and Rodenticide Act's definition of 'pesticide':

   > to exclude any article that is a 'new animal drug' within the meaning of the FD&C Act. Since the FIFRA definition of pesticide was amended in 1975, EPA has registered, as pesticides, articles that control the population of mosquitoes by killing them or interfering with their reproduction, which is consistent with FDA's and EPA's general agreement that articles or categories of articles that control the population of mosquitoes are most appropriately regulated as pesticides. This general agreement arises from a careful consideration of Congressional intent. (FDA 2017, 5)

   Presumably, both regulatory agencies were aware of the 1975 change to FIFRA, but it was only in October 2017 that the FDA ceded regulatory authority over the GE mosquito to the EPA.
5. We do not focus on whether risk assessment *is itself* appropriate and sufficient for making decisions about emerging technologies; others have written about that question elsewhere (Wickson 2007). Instead, we acknowledge that at least practically, risk assessments through the federal agencies will be the norm for decision-making for the foreseeable future. White House executive orders and federal agency policies give risk assessment a principal role in US regulatory policy.
6. This section draws on Meghani (2014).
7. For a carefully detailed account of the change in the FDA's risk assessments practices, see Hilts (2003).
8. According to Hilts, beginning in the 1980s, FDA reviewers routinely 'offered detailed advice (to developers of pharmaceuticals) on what studies were needed and how they should be designed' (2003, 228). Prior to the 1980s, FDA reviewers 'were not permitted to give company scientists guidance about what evidence would be sufficient to prove a drug's safety and effectiveness' (2003, 228).
9. For a critique of the 'clarification' process see Kuzma (2016).
10. While there are currently no guidelines for the risk assessment of animals with gene drives (as mentioned above), both the NASEM (2016) and the WHO use guidelines for 'regular' GE insects such as the OX513A mosquito to consider risk assessment for gene drives in animals.
11. A synthetic gene for the tetracycline transcriptional activator variant protein (tTAV) is introduced into the mosquito and acts as a tetracycline-regulated switch. High level expression of tTAV is deleterious to cells, as it represses normal transcriptional function. In the presence of

tetracycline, tTAV is repressed, so that the GE mosquito can be reared in the laboratory. In the absence of tetracycline, tTAV is active and kills the cells. The assumption is that the non-laboratory environment does not contain enough tetracycline for the GE mosquitos to survive.

12. In November 2016, Florida residents approved the release of the GE mosquitos on the basis of a public referendum but the town of Key Haven that was the site of the release rejected it. In the US, as of October 2017, no field trial of OX153A has taken place in the US.

13. Needless to say, the decision to classify the rDNA construct that is lethal to the animal in which it has been introduced (and its progeny) as a new animal drug has the odd result of the agency attempting to ascertain its safety for that organism because by law the FDA is obligated to determine whether new drugs are safe for the entities to which they are prescribed.

14. See for instance Oye et al. (2014) about other important variables that should be measured.

15. The exceptions are the GE mosquitos that are intended to function as pesticides.

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Notes on contributors

As a philosopher with a specialization in ethics, Dr *Zahra Meghani's* work is in the area of environmental ethics. She has a number of peer reviewed publications on the normativity of risk assessment of genetically engineered food. In particular, she examines the influence of neoliberalism on the US food regulatory system. Her aim is to identify and develop the theoretical underpinnings of a regulatory review process for genetically modified food that is transparent, unbiased, inclusive and democratic. She is also engaged in health care ethics research. The inequitable distribution of health care resources between different groups at the national and international level is the focus of her research. She is an Associate Professor in the Philosophy Department at the University of Rhode Island.

Jennifer Kuzma is the Goodnight-NCGSK Foundation Distinguished Professor in Social Sciences and co-director of the Genetic Engineering and Society Center at NC State University. Prior to this position she was a faculty member in science and technology policy at the Humphrey School of Public Affairs, University of Minnesota (2003–2013); study director at the National Academies of Science in Washington DC for genetic engineering and bioterrorism (1999–2003); and a AAAS Risk Policy Fellow at the US Dept. of Agriculture (1997–1999). She has over 100 scholarly publications on emerging technologies and governance; and has been studying genetic engineering and its societal aspects for over 25 years. She discovered that bacteria product isoprene, a precursor to natural rubber, during from her PhD work in biochemistry, and her postdoctoral work in plant molecular biology resulted in a publication in the journal Science. She has held several leadership positions, including the Society for Risk Analysis Council & Secretary, Chair of the Gordon Conference on S&T Policy, the FDA Blood Products Advisory Committee, and the UN WHO-FAO Expert Group for Nanotechnologies in Food and Agriculture. In 2014, she received the Society for Risk Analysis Sigma Xi Distinguished Lecturer Award for recognition of her outstanding contributions to the field of risk analysis. She has been called upon in national media for her expertise on genetic engineering policy issues, including recently in the Washington Post, Scientific American, New York Times, 2015 World's Fair exhibit, Nature, and National Public Radio.

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