

Procedurally Robust Risk Assessment Framework for Novel Genetically Engineered Organisms and Gene Drives

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Abstract

In this article, a new framework for improving risk assessments of novel genetically engineered organisms (GEOs) is developed and applied. The Procedurally Robust Risk Assessment Framework (PRRAF) provides a set of principles and criteria for assessing and enhancing risk assessment protocols for GEOs under conditions of high uncertainty. The application of PRRAF is demonstrated using the case of a genetically engineered mosquito designed to kill its wild population and therefore decrease disease transmission. Assessments for regulatory approval of this genetically engineered insect fall short of several PRRAF criteria under the principles of humility, procedural validity, inclusion, anticipation, and reflexivity. With the emergence of GEOs designed to spread in ecosystems, such as those with gene drives, it will become increasingly important for regulatory agencies and technology developers to bolster their risk analysis methods and processes prior to field testing. PRRAF can be used as a flexible guide for doing so within a variety of institutional, regulatory, and governance contexts.

Keywords: gene drive, gene editing, GMO, governance, risk analysis.

1. Introduction

Research is underway to develop genetically engineered (GE) strains of insects and other animals that are specifically designed for release in the wild to change, suppress, or eradicate the population of their wild-type counterpart. Gene drive organisms are a particular concern. They are designed using gene editing techniques that result in germline modifications that can be theoretically inherited by all offspring of the genetically engineered organisms (GEOs). Depending on how gene drives are designed, the release of even a few gene drive animals could result in the GE trait affecting the entire population of that species in the wild. Given the potential of gene drive organisms to alter populations within ecosystems, they could have wide-ranging ecological and health consequences. Therefore, the risk assessment protocol that is used for them must be capable of addressing this unique and difficult challenge. In this paper, a framework is developed to assist regulatory agencies, biotechnology developers, and other entities as they conduct risk analyses of GEOs (including gene drive animals and insects). The Procedurally Robust Risk Assessment Framework (PRRAF) includes a set of criteria and principles to assess risk evaluation protocols, with the larger aim of encouraging their improvement.

PRRAF is designed to improve risk assessments under conditions of high uncertainty and complexity, such as with gene drive organisms. Although gene drive organisms would result in inheritance patterns that are likely different from those associated with standard GEOs, they are similar to GEOs in other ways. As such, the 2016 National Academies of Science, Engineering, and Medicine (NASEM) report, *Gene Drives on the Horizon*, evokes the World Health Organization (WHO) guidelines for conducting risk assessments for standard GE insects (World Health Organization [WHO] 2014; National Academies of Science, Engineering, and Medicine [NASEM] 2016) to engage with the question of conducting risk assessment for gene drive insects. Likewise, in applying PRRAF in this article, the case study of a standard GE insect, OX513A, is used to inform PRRAF evaluations for future gene drive insects.

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1.1. Case study of genetically engineered (GE) mosquito regulation

Engineered gene drives result from recent advances in molecular biology, and in particular, gene editing techniques using CRISPR-Cas9. In cases of standard genetic engineering and gene editing, the introduced gene is usually carried on one of a pair of chromosomes and is inherited by approximately half of the offspring in the first generation. In contrast, gene drive systems enable an edited gene that is on a chromosome to copy itself onto the partner chromosome (Burt 2003; 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 spread through a large population within a relatively short time. Some of the motivations for using gene drives include reducing populations of pests (i.e. population suppression) or immunizing beneficial species against disease through population replacement (Esvelt *et al.* 2014). Fruit flies and mosquitos with gene drives, such as those based on the CRISPR-Cas9 system, have been successfully created and tested in laboratory cage experiments (Gantz *et al.* 2015; Hammond *et al.* 2016).

Gene drive organisms would be subject to regulatory review in the United States (US), although the regulatory path and agencies will depend on the engineered species, genes, and goals. But regulating gene drive organisms will be a challenge because they are designed to spread in the ecosystem and mate with the native population, whereas until now GEOs have been regulated in confined or contained settings, such as the laboratory, greenhouses, field trials, or certain agricultural systems. To get a sense of whether US regulatory agencies are prepared for the challenge of conducting risk assessments of gene drive animals, a risk assessment already conducted by the US Food and Drug Administration (FDA) for intentional environmental release of a GE insect is examined. This analysis also serves to demonstrate the use and relevance of PPRAF.

The US oversight approach to regulating biotechnology can be traced to the White House Office of Science and Technology Policy's 1986 policy statement, the *Coordinated Framework for Regulation of Biotechnology* (CFRB) (Office of Science Technology and Public Policy [OSTP] 1986). The CFRB identified the federal agencies that would be responsible for different kinds of biotechnology products, including GEOs (also known as genetically modified organisms [GMOs]). Under the CFRB, regulatory decisions have already been made for GE insects that contain self-killing systems, but not gene drives. Although until now no organism with a gene drive has been reviewed by regulatory agencies, both the US Department of Agriculture (USDA) and the FDA have reviewed GE insects designed for population suppression, which is one of the anticipated goals of gene drive technologies. For example, in 2008 and 2015, the USDA, acting under the authority of the Plant Protection Act (PPA), approved the release of GE pink bollworm and GE diamond back moth, two agricultural pests, for the purposes of suppressing their wild counterparts. The FDA is likely to have a key role in regulating gene drives in insects and other animals that are not plant pests or pesticides. The agency has broadly asserted authority over GE animals under the Federal Food Drug and Cosmetic Act (FFDCA) using the New Animal Drug (NAD) provisions (Food and Drug Administration [FDA] 2009). In fact, the FDA has exercised its regulatory claim on GE insects by reviewing Oxitec's *Aedes aegypti* OX513A. This GE mosquito is designed to eradicate its non-GE counterpart that transmits Dengue and the Zika virus to humans. In summer 2016, the agency approved field trials of the GE mosquito OX513A. The regulatory assessments for this approval are the subject of the PPRAF-guided analysis in this paper.

Regulatory review of GE insects is currently under flux, however. In 2017, the FDA issued a draft and then final guidance indicating that the Environmental Protection Agency (EPA), under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), would regulate GE mosquitos for pest control, but mosquitos for disease control would remain under the authority of FDA's NAD process (FDA 2017a). Ultimately, the developers of OX513A have removed the disease-control claims from this GE mosquito, and the product is now under review by the EPA for the general control of mosquito pests; however, the FDA would still review GE mosquitos and other GE insects or animals that make disease reduction claims or that are not pesticides (FDA 2017a). Therefore, FDA review of the GE mosquito is still relevant to other GE mosquitos, insects, or other animals that come under the FDA's authority.

In summary, the case of GE sterile insects like OX513A is relevant to the case of GE insects with gene drive systems in several ways: (i) the current US oversight system would require the same process of FDA review for GE mosquitos with gene drive systems that are meant for disease control (pending no new rules, guidelines, or statutes); (ii) it would also require the same regulatory documents unless higher requirements are mandated in the future; (iii) the intended impacts would be similar in that both technologies (OX513A and gene drive mosquitos) would be designed to reduce the population of disease carrying insects in the wild ; (iv) genetic transfer of

engineered genes to subsequent generations would occur in both cases in order to reduce the population; (v) the GE versus gene drive mosquitos would pose similar categories of ecological risk, such as decline of beneficial non-target populations, although the associated uncertainties might differ (e.g. NASEM [2017] have consistently recommended that it is the GE product's features, not the process by which the engineering takes place, that is relevant for risk analysis; OSTP 1986); and (vi) gene drives present a more rapid and thorough method of killing populations in the wild (as they would not require large and frequent releases of GE insects), but generally would result in the same risk endpoints.¹ Thus, the case of OX513A is an appropriate historical case study that, pending no unforeseeable changes to the US oversight systems, can be used to predict and evaluate how insects with engineered gene drives will be regulated in the future.

1.2. Risk governance for emerging biotechnologies

Several researchers have recognized the need for different risk governance approaches because of the uncertainty and novelty of products of synthetic biology, genetic engineering, and gene drives (Oye *et al.* 2014; Mandel & Marchant 2014; Akbari *et al.* 2015; Kuzma & Rawls 2016). They discuss the features of the respective categories of emerging biotechnologies broadly and offer principles, conclusions, or recommendations for their oversight. For example Mandel and Marchant (2014) make the case that existing “risk structures do not apply” for synthetic biology and then go on to discuss current regulatory gaps in jurisdiction. These authors (Oye *et al.* 2014; Mandel & Marchant 2014; Akbari *et al.* 2015) consider the wide breadth of products within technology categories (e.g. all gene drives, all synthetic biology). Oye *et al.* (2014) make expansive suggestions for all gene-drive technology, suggesting norms for ecological testing protocols, bolstering national security, and filling international governance gaps. These works are very useful as starting points for dialogue about emerging biotechnologies and oversight systems and support many of the arguments made in this article about the need for different federal risk analysis approaches. But their analysis does not address the product-specific nature of implementing oversight through federal risk assessment. As there are significant differences in specific products within these emerging biotechnology categories (Kuzma & Tanji 2010; NASEM 2017), the analysis herein takes a product-specific focus to evaluating oversight for GE animals that it is historical and evaluative in nature. The approach in this paper is most aligned with a retrospective policy analysis approach, whereby criteria are generated from normative, practical, and social science fields; applied to evaluate how a particular policy or policy system has performed in the past; and then used to forecast the need for changes to policy systems in the future (Coglianese 2005; Dunn 2015). This approach also differs from other analyses of gene drives in that it is specific to the risk analysis phase of oversight systems. For example Akbari *et al.* (2015), instead, recommend safety guidelines for conducting laboratory research on gene drives.

Engineering populations in the wild is becoming an increasingly realizable possibility, and a framework for evaluating and enhancing the validity and legitimacy of risk assessment methods and procedures under these conditions of high uncertainty and novelty is needed. In such situations, technical and expert-driven quantification of risk will be very difficult, fraught with uncertainty, and inadequate for decisionmaking (e.g. National Research Council [NRC] 1996; Wickson 2007; Kuzma & Besley 2008; NASEM 2017, pp. 115–120). This paper proposes PRRAF, a new multi-criteria analysis framework to guide the conduct of risk assessments for the release of novel GEOs into the wild.

A flaw in current regulatory risk evaluations for GEOs is rooted in the incorrect assumption that risk assessment is a value-neutral process and can be completely (natural) science-based. For instance, the US FDA's risk evaluations are predicated on the incorrect assumption that risk evaluations can be insulated from the influence of any ethical, political, economic, or other societal concerns. Researchers and think tanks have convincingly argued against this assumption (NRC 1994, 1996, 2009; Jasanoff 2003; Wickson 2007; Meghani 2014; NASEM 2017). NASEM, for instance, has noted that every step of the risk assessment process involves uncertainty because of the lack of complete knowledge (NRC 2009, p. 7), thus, risk assessors often must rely on assumptions (i.e. defaults) about evidence of risk and exposure that may have ethical or political significance. Moreover, risk evaluators' choices of endpoints (that they will assess) and methodology carry normative (i.e. ethical, political, socioeconomic, or cultural) weight (Kuzma & Besley 2008).²

To pilot PRRAF, in this article, the risk assessments of the GE mosquito, OX513A, submitted to and produced by the FDA for its regulatory approval are evaluated. However, the PRRAF can be applied to any agency’s or company’s risk analysis process to improve governance under conditions of high novelty, complexity, and uncertainty and within a variety of legal, regulatory, and oversight contexts in the US and internationally (Fig. 1).

2. Methodology

To construct the PRRAF, several frameworks from prominent think tanks and scholars for evaluating emerging risks, risk assessment, and risk governance processes were considered. Three frameworks that are meant for use in conditions of high uncertainty and that go beyond the traditional linear and technical quantification of risk were used (Fig. 1). These come from the fields of science and technology studies, risk analysis, and science and technology policy and are described in more detail below. From these, key principles of governance for emerging technologies, specifically, the principles of inclusion, reflexivity, anticipation, humility, and procedural validity were derived. To pilot PRRAF, qualitative analysis was used on documents submitted to or provided by the FDA for OX513A regulatory approval that were publicly available as of July 2017 (Oxitec 2016; FDA 2016a,b,c).

2.1. Origins of the Procedurally Robust Risk Assessment Framework (PRRAF)

A key science and technology studies researcher, Sheila Jasanoff, has argued that in the face of dispersed, unknown, uncertain, ambiguous, uncontrollable, and context-dependent scientific pursuits, the criteria of “accountability” must supplement traditional evaluations of safety, efficiency, and efficacy for public justification of science and technology (Jasanoff 2003). In developing this framework, she proposes that instead of an attitude of unjustified confidence in technological development, decisionmakers and technology developers should adopt an attitude of humility. She issued the following challenge: “Can we imagine new institutions, processes, and methods for restoring to the playing field of governance some of the normative questions that were sidelined in celebrating the benefits of technological progress?” (Jasanoff 2003, p. 226). With this motivation, approaches that are based on humility are contrasted with those based on hubris. In the interest of adopting an attitude of humility during risk assessment of GEOs, PRRAF entails: (i) public inclusion into the framing of risk assessments, (ii) the examination of the social foundations of vulnerability to risks, (iii) the identification of the distribution of

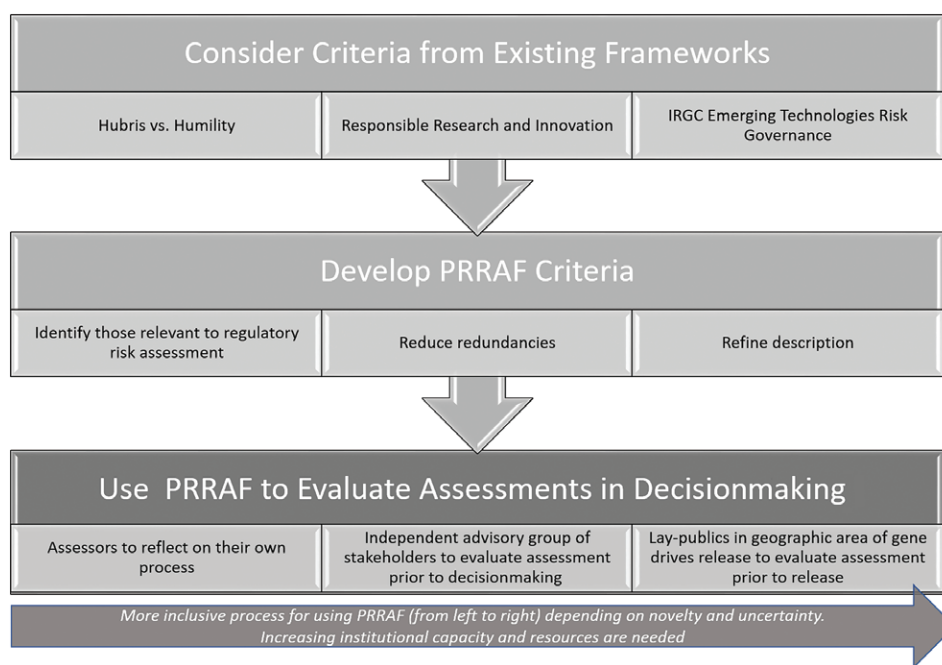


Figure 1 Origins and Uses for the Procedurally Robust Risk Assessment Framework (PRRAF). IRGC, International Risk Governance Council.

impacts from the new technology, and (iv) learning as a part of citizen deliberation (Jasanoff 2003). The attitude of humility that is part of PRRAF is a way to counterbalance the neoliberal leanings of the CFRB and the FDA (Meghani & Kuzma 2017).

The second framework that informs PRRAF focuses on emerging risks, which are defined by the International Risk Governance Council (IRGC) as those with high uncertainty and ambiguity and for which prediction is difficult (IRGC 2015). The deployment of gene drives and GE insects for the purposes of population suppression (like OX513A) fall into the emerging risks category. Data is very limited, systems are complex, there are few precedents, and the impact of the genetic modification may not be evident for decades. For these situations, evaluating the “substantive validity” of risk assessments – where outcomes of the risk assessment are compared to what happens in reality – is not really possible, especially prior to any environmental release. Therefore, “procedural validity” of the risk assessment becomes even more important than attempting to ascertain the substantive validity of particular risk evaluations. Thus, PRRAF includes procedural criteria suggested by the IRGC for evaluating risk assessments.

The third framework that influenced PRRAF is the Responsible Research and Innovation (RRI) approach. Social science and policy scholars have proposed four pillars for this concept: anticipation, inclusion, reflexivity, and responsiveness (Stilgoe *et al.* 2013). Anticipation with respect to responsible research and innovation entails asking the “what if...?” questions. The aim is to take into consideration contingency, what is known, what is likely, what is plausible, and what is possible. It differs from traditional hazard identification in risk assessment by stretching the boundaries of typical thinking about the probable under current conditions to broader thinking about the possible under a variety of future scenarios and changing environmental, social, or cultural conditions. The RRI approach also advocates inclusiveness, specifically, engaging new voices in discussion about the ends and the means of innovation. Reflexivity is also part of the RRI approach. It requires that technology developers and societies examine their own activities and assumptions to gain an awareness of the limits of their knowledge and framing biases. Responsiveness involves the capacity to change the shape or direction of innovation in response to stakeholder and public values and circumstances. Although RRI focuses more on upstream technology development than on the regulatory risk assessment stage, it was adapted to develop PRRAF with criteria from RRI that relate to risk assessment processes.

The three frameworks – Jasanoff's (2003), IRGC's (2015), and RRI (Stilgoe *et al.* 2013) – overlap to an extent. In addition, some elements are most appropriate for post-risk management or recovery phases of the deployment of emerging technologies. As such, criteria from these three frameworks that were similar were combined, and the set was reduced to those that could be used to evaluate the risk assessment process germane to federal regulatory agencies and other organizations engaged in decisionmaking. Thus, our framework is more tailored and comprehensive than any of the predecessors for the purpose of regulatory risk assessment processes. These origins and options for use of PRRAF are summarized in Figure 1. PRRAF rests on five categories of principles; humility, reflexivity, procedural validity, anticipation, and inclusion, and 18 specific criteria (Table 1).

2.2. Principle of humility

A limited number of controlled laboratory experiments cannot fully assess uncertainties and complex, complicated risks. For that reason, Jasanoff proposed that risk assessors and technology developers eschew unjustified confidence in risk assessments and adopt an attitude of humility (Jasanoff 2003). Specifically, vulnerability and exposure to risk (and harm) are a function of social and behavioral factors, both at individual and group levels. Therefore, the principle of humility requires assessment of the distributive impact of risks (and harms) among different groups and communities. Because risk assessments are normative endeavors, the humility principle requires that risk assessments take into account the ethical, political, socio-economic, and cultural concerns expressed by public groups about the new biotechnology in the framing of risk assessments. Knowledge limitations also make it reasonable that risk assessors utilize the learning potential of public engagement. This view is supported by NASEM reports on gene drives (NASEM 2016) and future biotechnology products (NASEM 2017), as well as earlier reports (NRC 1996).

Table 1 Evaluation of the FDA-Oxitec risk analysis of the Oxitec GE mosquito

Criteria	Final FDA-Oxitec EA & FONSI
<ul style="list-style-type: none"> Principles 	
Principle of Humility [†]	Minimal to none
<ul style="list-style-type: none"> Assess social and behavioral foundations of vulnerability to risk 	<i>Minimal</i>
<ul style="list-style-type: none"> Consider the ethical, political, and other social dimensions of the distributive impact of risks among different groups and communities 	<i>Minimal</i>
<ul style="list-style-type: none"> Elicit public input into framing of risk analysis that is open to non-technological alternatives 	<i>None</i>
<ul style="list-style-type: none"> Promote mutual learning as object of deliberation in risk analysis 	<i>None</i>
Principle of Inclusion [†]	Minimal to none
<ul style="list-style-type: none"> Engage multiple interested and affected parties in discussion of ends and means of innovation 	<i>None</i>
<ul style="list-style-type: none"> Elicit the input of interested and affected parties to scope the risk problem and at key junctures in risk assessment 	<i>Minimal</i> [‡]
Principle of Reflexivity	Minimal to none
<ul style="list-style-type: none"> Examine assumptions and framing in risk analysis 	<i>Minimal</i>
<ul style="list-style-type: none"> Acknowledge alternative explanations to the data and analysis 	<i>None</i>
<ul style="list-style-type: none"> Reflect on quality of organizational processes used for risk analysis 	<i>None</i>
<ul style="list-style-type: none"> Reflect on meaning of errors to outcomes and reputations of assessors 	<i>None</i>
Principle of Procedural Validity	Minimal to none
<ul style="list-style-type: none"> Assess the quality of the risk analysis process that led to the outcomes 	<i>None</i>
<ul style="list-style-type: none"> Evaluate scientific validity of the approaches used in risk analysis 	<i>Minimal</i>
<ul style="list-style-type: none"> Proceed with openness and transparency in conduct of risk analysis 	<i>Minimal</i>
<ul style="list-style-type: none"> Ensure consistency in interpretations of data and information 	<i>Minimal</i>
<ul style="list-style-type: none"> Use all available, relevant information including subjective probabilities 	<i>None</i>
<ul style="list-style-type: none"> Consider the acceptability of the results and interpretations to those who provide inputs to the analysis 	<i>None</i>
Principle of Anticipation	Minimal to None
<ul style="list-style-type: none"> Consider contingencies of what is known, plausible, possible, and unknown for the future 	<i>Minimal</i>
<ul style="list-style-type: none"> Account for changing future conditions at different timescales 	<i>None</i>

[†]Mainly in comment and rulemaking process between the draft and final environmental assessments (EAs) and findings of no significant impact (FONSI). [‡]Note that there is a deep connection between humility and inclusion in the engagement of different and broader ranges of parties in the risk assessment. FDA, Food & Drug Administration; GE, genetically engineered.

Taking the elements from Jasanoff's humility approach and applying them to risk assessment, four operational criteria for regulatory risk assessors were included in PRRAF: assess social foundations of vulnerability to risk, consider distributive impacts on different populations, elicit public input into framing of risk analysis, and promote mutual learning as an object of deliberation in risk analysis.³ Under the humility principle, public input into "framing" could mean the choice not to proceed with the technology but to pursue other mosquito control methods.

2.3. Principle of inclusion

As emerging biotechnologies are characterized by a paucity of knowledge and significant uncertainty, it makes sense to draw on as many as possible available sources of knowledge for the purposes of risk assessment. Thus, another foundational principle of PRRAF is inclusiveness. It has a deep connection to humility in the recognition that outside perspectives (especially those that challenge the dominant position) would be more likely to produce a rigorous risk assessment than one that has not been subject to such scrutiny. Some of those constituencies may have independent scientific and risk assessment experts who should also be part of the dialogue (NRC 1996). The principle of inclusion places an obligation on risk assessors to elicit input from interested and affected parties to scope the problem and at key junctures in the risk assessment process (NRC 1996). This inclusiveness criterion serves to "force" critical dialogue about the normative commitments that should shape particular risk assessments. They would be identified and "placed on the table" as topics of deliberation. Involvement of a diversity of stakeholders, beginning with the problem formulation and framing stage, would avoid the echo chamber effect that could compromise risk evaluations because alternatives or the possibility or consequence of failure were

discounted or overlooked. Therefore, there are epistemic and ethical benefits to adopting the principle of inclusiveness (NRC 1996; Wickson 2007; Meghani 2014; NASEM 2016, 2017).

This principle also suggests that risk assessors should engage in dialogue with affected communities and groups about the goals of the biotechnology and the means by which those aims are to be realized. For example, deploying GE insects in a heavily populated city for suppression of the wild counterpart, could have different aims, depending on whether or not there are reported instances of the insect transmitting a disease in that area (NASEM 2016). Derived from the RRI framework (Stilgoe *et al.* 2013), inclusion also involves engaging multiple interested and affected parties in discussion of the ends and means of innovation. Through this discussion, participants will better understand the methods, motivations, and relationships of actors that deploy GEOs in order to contextualize risk assessments.

2.4. Principle of reflexivity

The criterion of reflexivity requires that risk assessors scrutinize risk evaluations in a variety of other ways (Jasanoff 2003; Stilgoe *et al.* 2013). In conjunction with public constituencies, they should interrogate the following aspects of risk assessment: background assumptions; problem framing; organizational processes; significance of error; the differentiated impact of errors on groups and communities, as well as the environment; and the acceptability of risks to those who provide inputs. Moreover, they should explore alternative explanations for their data and conclusions. Reflexivity at the institutional level has been described as “holding a mirror up to one’s own activities, commitments and assumptions, being aware of the limits of knowledge and being mindful that a particular framing of an issue may not be universally held” (Stilgoe *et al.* 2013, p. 1571). Four criteria were articulated from this principle: examining assumptions and framing in risk analysis, acknowledging alternative explanations to the data and analysis, reflecting on the quality of organizational processes used for risk analysis, and considering the meaning of errors to outcomes and the reputations of assessors (Table 1).

2.5. Principle of procedural validity

In many situations associated with the release of novel GEOs, including GE or gene drive mosquitos, it will be nearly impossible to validate risk assessments with field trial data prior to release. Although some intermediate risk endpoints can be measured in the field (e.g. number of female mosquitos released), impacts on biodiversity or gene flow to nontarget organisms will take time to manifest themselves or will occur at a low frequency. Furthermore full-scale release of a GEO is likely, and in fact is designed, to have different consequences than field trials. Thus, the process of risk assessment becomes even more important than it would be otherwise. Under such conditions, the IRGC has proposed that risk assessors should attempt to evaluate the quality of their risk assessment process in addition to the quality of the results (IRGC 2015), terming this “procedural validity.” As part of procedural validity, risk assessors should: (i) consider the quality of their risk evaluation process; (ii) be open and transparent (about value-based assumptions, methodology, and data); (iii) use all available information, including subjective probabilities (which might be the only way to estimate risk under high uncertainty); and (iv) consider the acceptability of the results to those who provide input into the assessment. These four elements, along with ensuring the scientific validity of the approaches used in risk analysis and the consistency in interpreting data and information (also suggested by IRGC for all risks), constitute the six criteria in the PRRAF under procedural validity.

2.6. Principle of anticipation

Inclusiveness and (scientific) humility entail respect for the principle of anticipation. In constructing the requirements of this principle, the RRI framework, as well as recommendations for best and worst-case risk scenario construction in the IRGC framework, were used (Stilgoe *et al.* 2013; IRGC 2015). Motivations for the anticipation principle come from historical experience in that “the detrimental implications of new technologies are often unforeseen, and risk-based estimates of harm have commonly failed to provide early warnings of future effects” (Stilgoe *et al.* 2013, p. 1570). As part of PRRAF, the anticipation principle sets the standard that risk assessors must address contingencies, asking “what if” questions, and consider a spectrum of worst-case scenarios over short and long-term time scales. Uncertainty about the impacts of the novel biotechnology and the deployment

of GEOs necessitates the construction of risk assessments that include timescale as a variable. Ecological consequences can take years, even decades, to manifest themselves. Furthermore, environments change over time. Therefore, the choice of time scale in a risk assessment is a normative one. The principle of anticipation is operationalized for risk assessment with two criteria: (i) consideration of contingencies of what is known, plausible, possible, and unknown for the future; and (ii) accounting for changing future conditions at different timescales (Table 1).

2.7. Execution of policy analysis approach

Using the 18 criteria listed in Table 1, a policy analysis approach was used to evaluate the regulatory risk analysis of the case study of GE mosquitos designed for disease control. In this article, the case study is analyzed based on the author's expertise in consultation with colleagues and other experts. Ideally in a governance system, more voices would judge whether a risk assessment process meets PRRAF criteria and principles. For example, PRRAF could be used by an independent, external advisory group to evaluate risk analyses used for regulatory decision-making. Under conditions of low capacity or a lack of infrastructure for external engagement, at a minimum, GEO developers and regulators could use PRRAF to reflect on their own risk assessments (Fig. 1).

In this article, evidence of conformity to the principles in PRRAF follow a policy analysis approach, and the regulatory decisionmaking system is evaluated in qualitative ways with regard to whether it satisfies the criteria (Bardach & Patashnik 2015; Dunn 2015). This analysis takes a product-specific focus and considers how that product was overseen by the regulatory system according to principles and criteria from the literature. It is historical in evaluating past policies and programs (retrospective policy analysis). The analysis is then used to forecast the need for changes to policy systems in the future (a prospective policy analysis) (Bardach & Patashnik 2015; Dunn 2015). The results are then used to suggest improvements for future regulatory assessments of GEOs, such as those associated with gene drives in disease-controlling insects, for which the Oxitec case study is the closest existing analog.

Multi-criteria decision analysis (MCDA) evaluation approaches (Linkov & Moberg 2011) also have been used to evaluate oversight systems for GEOs (Kuzma *et al.* 2008, 2009). MCDA is usually performed quantitatively and with weighting of criteria (Linkov *et al.* 2006; Linkov & Moberg 2011). The analysis in this paper is qualitative, documenting evidence and text to support the evaluation of the regulatory risk analysis for GE mosquitos using the PRRAF criteria. However, there are similarities between policy analysis and MCDA in terms of their use of criteria to examine policies or decisions. In this way, the methods in this paper overlap with both approaches.

To apply the criteria, the environmental assessments (EAs) and findings of no significant impact (FONSIs) for the GE mosquito risk assessment are examined according to the stages of ecological risk assessment (Environmental Protection Agency [EPA] 1998) to organize the evaluation. Those stages of ecological risk assessment are: (i) problem formulation and framing, (ii) exposure and effects assessment, and (iii) risk characterization (EPA 1998).

3. Results

In this section, the statutory and regulatory context for the Oxitec GE mosquito risk assessment, which affects the focus and problem framing of the assessment, is first considered. PRRAF is then used to analyze exposure and effects assessments and risk characterization expressed in the regulatory risk analysis documents. The evaluation revealed that the risk assessment process for the Oxitec GE mosquito falls short of the PRRAF principles in multiple regards. Based on the analysis and critique, it is suggested that the agency's risk evaluation protocol should be revised and enhanced to meet the challenges of future GE insects, GE animals, and those with gene drives.

3.1. PRRAF evaluation of problem framing and formulation

In this section, the regulation of GE mosquitos under the Food, Drug & Cosmetics Act (FDCA) and the National Environmental Policy Act (NEPA) is considered as it relates to problem framing and formulation of the risk analysis and the institutional context that affects this stage.

3.1.1. Food, Drug & Cosmetics Act process of approval

In 2009, the FDA published guidance outlining its regulatory policy for GE animals, including insects. The agency used the *Guidance* to claim regulatory authority over GE animals as “new animal drugs” (NADs) under the FDCA. The FDCA conceptualizes any non-food article that is intended “to affect the structure or any function of the body of man or other animals” (FDA 2017b) as a drug. The agency argued that the rDNA constructs introduced into GE animals aim to impact their bodily structure or function, and therefore, they qualify as NADs. The FDCA gives the FDA the authority to evaluate *the safety and the efficacy* of the drug (in other words, to investigate whether it is safe for the animal and does what it is supposed to do). Under the 2009 *Guidance* (FDA 2009, revised 2015), sponsors of GE animals are obligated to submit a NAD Application to the FDA’s Center for Veterinary Medicine. The subject of the NAD Application is the rDNA construct at a particular location in the genome, thus, the agency technically has regulatory authority over that article in the GE animal, not the GE animal (FDA 2009, p. 6). However, “as a short hand in this guidance document,” the FDA “sometimes refer(s) to regulation of the article in such GE animals as regulation of the GE animal” (FDA 2009, p. 7). In January 2017, the FDA put forth a revised guidance document that expands the scope of its authority to include gene-edited animals and other animals with “intentionally altered genomic DNA” (FDA 2017b).

One flaw in the NAD process for risk assessment of GE animals is that it places commercial interests over transparency and early inclusion of public health and environmental concerns. For example, it is standard practice for companies to use the trade secrets to classify the information that they submit as part of their application to regulatory agencies as confidential business information (CBI). But CBI can be exercised to an even greater degree in the NAD process, as the FDA is *prohibited* from disclosing even the existence of a NAD file before NAD approval has been published in the *Federal Register* (21 CFR 514.11b; Otts 2014). This means that (as in the GE mosquito OX513A case) future developers of GE animals with gene drives would not have to share their risk assessments with the public until the agency is poised to make a decision about them (when a draft EA and FONSI are complete and posted). The decision to favor the interests of the commercial sector (over the public’s interest in open sharing of data) violates PRRAF’s principles of inclusion, including public input for framing and co-learning with citizens before and during the risk assessment process (see Table 1).

Oxitec formally submitted its application for the GE OX513A mosquito to the FDA under the investigational new animal drug (INAD) provisions of the FDCA, and in March 2016, the agency published its draft assessment documents for the GE mosquito OX513A – specifically, an EA and FONSI in order to approve field trials (which are treated as clinical trials under investigational NAD or INAD authorities) (Oxitec 2016; FDA 2016a). These documents were open for public comment, and then finalized in August 2016 without substantial changes to the conclusions or the recommendation to approve the field trial (FDA 2016b,c). Even so, one could argue that some inclusion of the public did occur during the federal register notice and comment period, as the FDA must consider (but not necessarily incorporate) relevant public comments in revision of the EA and FONSI documents according to the Administrative Procedures Act. However, comment periods are known to be one of the least inclusive forms of public engagement, with problems of representativeness, responsiveness, and access (Golden 1998; Rowe & Frewer 2000; Coglianese 2005). Public comment on rules does not meet the inclusion criteria in the PRRAF, which are inspired by deeper levels of participation and engagement (as described in NASEM 2016, 2017 reports and the RRI framework, NRC 1996; Stilgoe *et al.* 2013). NASEM (2017) recommend inclusion of outside perspectives in the conduct of the risk assessment itself, especially when uncertainty and novelty are high (NRC 1996). It is also the recommendation of the three groups upon which the PRRAF is based (Jasanoff 2003; Stilgoe *et al.* 2013; IRGC 2015). Taking public comment only after the assessment had been conducted and not during the scoping or interpretation of risk at intermediate assessment steps is not congruent with principles of PRRAF or recommendations for robust risk characterization (NRC 1996; NASEM 2016).

After the EA and FONSI were finalized, the GE mosquitoes were slated for release in the US Florida Keys, where cases of Dengue have been documented and concerns about Zika were growing. However, before allowing release in the state, the local Florida Keys Mosquito Control Board decided to consider the results of a public referendum vote on the GE mosquito, which took place on 8 November 2016. Ultimately, the residents of the Florida Keys approved the release of the GE mosquitos by a majority in this referendum, although Key Haven, the town proposed for the release, rejected it; thus putting a halt to the release. Oxitec has been forced seek a new site for release, which as of late 2018 is ongoing.⁴

3.1.2. National Environmental Policy Act procedural analysis

NEPA is another statute that influences how problems are defined for risk assessment for GE animals. While the FDA's regulatory authority comes from the FDCA and the NAD provisions in the case of GE animals, the agency is obligated to abide by the NEPA. The NEPA is triggered whenever the FDA considers field trials for GE animals. According to the FDA 2009 *Guidance*, to marry the NAD process with the NEPA, the agency made the decision to treat field trials of GE organisms as analogous to clinical trials of INADs (FDA 2009). After successful trials, the developer submits a NAD to acquire permission for interstate commerce. The clinical trial categorization for field trials of the GE mosquito presents a unique challenge. A clinical trial to identify the effectiveness of the GE mosquito (a "drug") in reducing the wild *A. aegypti* mosquito population means that the GE organism must *spread and mix with* the wild populations of its species, but traditionally, field trials aim to *contain and confine the organism being tested to prevent its spread*. Mosquitos are highly mobile. Field trials are supposed to occur in a limited area, but containment to a specified area is unlikely, especially with insects that fly and persist. This is a paradox, and instead the impact of the GE mosquito OX513A on other species and ecosystems should be the primary matter of concern of risk assessment. The authorities used by the FDA do not seem to fit the context of risk assessment for GE mosquitos given their focus on "drug" efficacy and safety, not ecosystem and health impacts. This deficiency relates to inadequate reflexivity in problem framing of risk assessment, a violation of a criterion of the PRRAF.

It is primarily because the FDA is obligated to abide by NEPA that the FDA attempts to ascertain the larger environmental significance of the products it regulates and encourage product sponsors to be attentive to them in their plans for risk management. However, NEPA is a procedural (process-based) law, in that it requires federal agencies to review and document the environmental impact of any significant federal action; but regulatory agencies do not technically have authority under NEPA to prohibit proposed actions, such as GE product release (40 CFR §1500-1508). NEPA has designated three levels of environmental review with increasing detail and rigor: categorical exclusions, EAs and FONSI, and environmental impact statements (EISs). The agency takes a position prior to assessment in choosing one of these three routes based on its view of the anticipated environmental impacts.

Environmental and consumer groups have been dissatisfied with the quality of the FDA's compliance with NEPA with respect to GE organisms. For example, they have filed lawsuits against the agency for its decision to approve AquaBounty's GE salmon because:

[T]he inadequate EA (i.e. Environmental Assessment for the GE salmon), FONSI, and attendant decision not to prepare a comprehensive EIS are the result of FDA's failure to take the legally required "hard look" at these direct, indirect, and cumulative impacts of the agency's decision to allow mass production of AquaBounty's GE salmon, and are arbitrary, capricious, and contrary to NEPA. (Keat *et al.* v. US DHHS FDA 2016)

The US Department of Agriculture has also come under attack from consumer and environmental groups for not abiding by the spirit of NEPA (Cowan & Alexander 2013).

The choice to not prepare a full EIS suggests that the FDA did not proceed with the appropriate degree of procedural validity and humility. If the agency had followed the principles advocated by PRRAF, then given the uncertainty and novelty of the GE organism it would have prepared an EIS, the most rigorous choice under NEPA. In addition to a fuller consideration of ecological impacts, a NEPA EIS analysis also requires an analysis of socio-economic and distributional impacts, and more in-depth public input processes, coming closer to satisfying the principles of humility and inclusion of the PRRAF.

Permitting the release of the GE mosquito without an EIS suggests that the FDA may have been influenced by the neoliberal mandate of advancing the biotechnology industry's interests (Meghani & Kuzma 2017). The agency's risk assessment would have had greater procedural validity if (in an EIS) it had more rigorously examined the potential ecological impacts and greater humility had it considered societal ramifications (criterion under humility in Table 1) and tradeoffs of alternatives (criterion under humility in Table 1 "Elicitation of the input of interested and affected parties for scoping the risk problem"). The FDA has not carefully considered either reputational risks or acceptability to those who may provide input (both are part of the procedural validity criterion) (Table 1). It also did not engage external experts, stakeholders, or citizens as it conducted the assessments, violating the principle of inclusion and failing to adopt an attitude of humility toward risk assessment through citizen learning or public input in framing of the issues.

Moreover, some biologists have criticized the FDA for not deferring to the Department of Interior's Fish and Wildlife Service (FWS) and the National Marine Fisheries Services (NMFS) because of their expert knowledge of ecological issues and because they are responsible for administering the Endangered Species Act (ESA, 16 U.S.C. § 1531–1544). The Lacey Act (18 U.S.C. § 42) gives the FWS regulatory authority to bar the importation and transportation of species “injurious to human beings, to the interests of agriculture, horticulture, forestry, or to wildlife or the wildlife resources of the US.” But that agency has not been given the opportunity to be substantially involved in the regulation of GE animals and it has criticized the FDA's risk assessment of Aquabounty Salmon (Earthjustice & Center for Food Safety 2013). The FDA's decision to exclude agencies with the appropriate expertise from the risk assessment process undermines the procedural validity of its risk assessment as the quality of the scientific process lacks rigor.

A review of the (publicly available) documents submitted by Oxitec to the FDA (FDA 2016a,b,c; Oxitec 2016) shows that the biotechnology company did not provide the FDA with field data on the ecological monitoring of nontarget organisms or other environmental endpoints from prior releases of the GE mosquito in other countries, nor is it required to collect such field data under the new trial in the US given the focus under the NAD provisions on safety and efficacy. However, now that Oxitec is searching for a new site, the FDA has the opportunity to prepare a full EIS, which would provide an opportunity for more comprehensive analysis of the possible impact of the release of the GE mosquito on nontargets and to include its social and economic significance (thus paying more attention to the principle of humility and criteria of assessing social foundations of vulnerability to risk and considering distributive socio-economic impacts on risks to different populations).

The legal authority of the FDA applies only to whether the rDNA construct is safe for the GE animal in which it has been introduced (“drug” safety) and whether the GE animal results in the suppression of the population of its wild-type counterpart (“drug” efficacy). Needless to say, the safety of the rDNA construct for the GE mosquito is irrelevant in this context. The germline genetic modification introduces a change in the organism such that its progeny dies without tetracycline, which is not always present in sufficient quantity in a non-laboratory environment. Therefore, it makes little sense to evaluate the safety of the genetic modification for the animal itself, as it is designed to kill it. The second serious limitation of the INAD clinical/field trial is that Oxitec's environmental assessment is focused on the efficacy of the GE mosquito to kill off the wild population. The INAD application and focus does not require that the company collect field data on the potential or unanticipated impacts on local ecosystems (including nontarget organisms), horizontal gene flow, and many other endpoints that are of relevance. Both the draft and final EAs state that the primary and secondary goals of the assessments relate to the efficacy of population suppression (FDA 2016b, pp. 38–39; Oxitec 2016, pp. 37–38). Nontarget impacts are discussed in the final EA, but there are no requirements for data collection on these impacts in the INAD process. Thus, the FDA and Oxitec are making a choice that has ethical and political significance about whether to allow field trials (under an INAD) and move to full-scale release, sale, and transport. This limited problem framing with no public input violates PPRAF, specifically, the principles of humility (criteria of public input into risk analysis framing) and inclusion (criterion of elicitation of the input of interested and affected parties for scoping the risk problem).

Oxitec has previously evaluated the efficacy of population suppression in other countries where GE mosquito release has already taken place, namely Brazil, Cayman Islands, Malaysia, and Panama. In field trials in these locations, the GE mosquito has reduced the target mosquito population (Nimmo & Beech 2015). However, human disease reduction from these releases, the ultimate goal, has not been demonstrated (Nimmo & Beech 2015). The definition of efficacy as mosquito control rather than disease reduction is another normative choice that was determined without public input or reflexivity. Furthermore, in standard clinical trials, participants must be fully informed of the risks to them. In the case of GE mosquito trials (treated like clinical trials under the NDA and NEPA process), the FDA did not require informed consent. This constitutes another violation of the PPRAF, specifically, a direct affront to the principle of inclusion.

In conclusion, the institutional context, both legal and procedural, affects the problem framing stage of risk assessment, which in the case of the GE mosquito is deficient with regard to several principles of the PPRAF.

3.2. PPRAF evaluation of exposure and effects stage of risk analysis

Risk is commonly defined in the field of environmental or health risk analysis as the combination of the likelihood of exposure and the severity of the consequences. In more complex systems, such as ecosystems, risk can be

thought of as “risk scenarios” (Kaplan & Garrick 1981) that address three questions: what can happen; how likely is that to happen; and if it does happen, what are the consequences (NASEM 2017)? In the NASEM report on gene drives, ecological risks are described as “the probability of an effect on a specific endpoint or set of endpoints due to a specific stressor or set of stressors” (2016, pp. 112–133), with the *effect* as potential beneficial or harmful outcomes; and an *endpoint* as a societal, human health, or environmental value that is to be managed or protected.

All of these ways of looking at risk are congruent in that they include a final definition of risk that involves combining the probability of an adverse event (e.g. likelihood of exposure) with the severity or magnitude of the effects from that event in order to assess risk endpoints of human or another population’s death, illness, injury, or decline. Unfortunately, the final EA (not so much the draft EA) varies from the norms of risk analysis by conflating the estimation of exposure pathways, events, or effects with estimations of human/animal health or environmental risks (compare Tables 9 in Oxitec 2016 vs. FDA 2016b). This problem is discussed further in the next section on risk characterization. However, first the two major components of the definitions cited above are examined, exposure and effects; and how the two EAs deal with evaluating these with regard to the GE mosquito.

The GE mosquito OX513A strain contains a synthetic gene for the tetracycline transcriptional activator variant protein (tTAV) (FDA 2016b). High levels of tTAV are deleterious to cells as it represses normal transcriptional function. However, in the presence of tetracycline, tTAV expression is suppressed. This means that the GE mosquito can be reared in the laboratory using tetracycline, but if it is an environment without adequate levels of the chemical, most of the larvae will not survive (more on this later). Effects evaluated in the EA and FONSI include:

[T]oxic effects in humans or non-target animals or allergenic effects in humans (from direct contact with tTAV); the effect of tetracycline (from rearing the GE mosquitos and disposal) on the environment; effect on flora of the GE mosquito release; effects on predators of the GE mosquito; effects on decomposers; and effects on endangered or threatened species. (FDA 2016b, Table 9).

Exposure pathways or events considered in the final EA include the:

[T]ransfer of the rDNA construct to humans or non-target animals (through predation, or bites); increase in population of other mosquitoes that may contribute to the increase of diseases; development of anti-microbial resistance; release of GE female mosquitos (as opposed to GE male mosquitos only); failure of the introduced traits;; persistence of the GE mosquito at the trial site; and interbreeding with related mosquito species. (FDA 2016b, Table 9)

Space is too limited in this article to point out the strengths and weaknesses of how the EA and FONSI evaluate each of these exposures and effects. Many of the human and animal health risks depend on the presence, survival, and spread of the GE mosquito. Therefore, how the FDA-Oxitec risk assessment considers these key intermediate steps in risk pathways are evaluated using the PRRAF.

3.2.1. Initial presence of the GE mosquito

Female *A. aegypti* mosquitos are the ones that bite, so in the interest of not increasing the number of biting mosquitos, the company plans to release male GE mosquitos. However, Oxitec cannot achieve 100 percent efficiency in its separation of males and females in the laboratory (FDA 2016b; Oxitec 2016). The draft EA (Oxitec 2016, p. 34) and final EA (FDA 2016b, p. 36) state that batches of GE mosquitos must contain less than 0.2 percent females before the company will allow their release. In the final EA, this percentage is used to estimate the number of GE females that would *initially* be released (first generation) in the environment over the course of the field trials (FDA 2016b, p. 39).

The total number of GE mosquitos (males and contaminating females) that the company plans to release depends on findings from phases I and II of the field trial, which are designed to estimate the number of wild-type *A. aegypti* mosquitos in the field trial area and conduct short-term releases (8–10 weeks) to monitor the ratio of wild-type to GE mosquitos via collection traps. For the first release, the goal is to achieve an initial mating fraction of ≥ 0.5 (i.e. the number of GE mosquitos released to the number of wild-type mosquitos in the trial area). This approximately amounts to a ratio of *male* GE mosquitos to *female* wild-type mosquitos of 1:1. From

this strategy and previous data on this mosquito species in other ecosystems, Oxitec states in the final EA: “we are able to estimate the minimum number of OX513A mosquitoes that might be released.” 14,352,000 GE mosquitoes over the 104 week trial period (FDA 2016b, p. 39–40). Based on the 0.2 percent adventitious presence of GE females in released “male” batches, that amounts to “less than 62 female mosquitoes released per person” in the target area over the course of the trial (FDA 2016b, pp. 39–40). Expressed another way, the final EA states that the total would be “0.6 female mosquitoes per person per week” and 2.4 GE female mosquitoes per household per week (assuming four people per household) (FDA 2016b, pp. 39–40).

The methods used to generate and interpret the data on GE female releases in the final EA are problematic given the principles of the PRRAF. First as Oxitec admits, the company uses a “minimum” point estimate (without uncertainty and variability analysis) for the number of GE mosquitoes released, thus downplaying the numbers. From the standpoint of procedural validity, they are not using the best risk assessment methods, which would instead incorporate a probability distribution for a range of values for the number of GE mosquitoes released and generate best and worst-case scenarios. Instead, the final EA falls short of the procedural validity criteria of “using all available, relevant information including subjective probabilities” and of “evaluating the scientific validity of the approaches used” (Table 1). The principle of humility is also not satisfied as a humility-based approach would recognize that the mosquitoes are not likely to be spread equally among households, but may reside in areas of standing water in greater numbers, especially around poorer homes that do not have the time or resources to keep well-maintained lawns or living spaces (this analysis is based on the humility rubric that requires taking into consideration social and behavioral factors affecting risk and distributional impacts). The principle of anticipation is partially recognized in that the company acknowledges that the number released will vary with changing conditions, but they do not account for this variability in the estimates of the release of total or female GE mosquitoes. The process of deriving the estimate was also a seemingly closed one including only the company and agency staff, thus violating the principle of inclusion to elicit the input of interested and affected at key junctures in the risk assessment. Outside experts could have been invited to participate in an expert elicitation to estimate probabilities, as is done in other types of ecological risk assessments (Linkov *et al.* 2006; Murphy *et al.* 2010; Linkov & Moberg 2011).

In addition, another way to express the same data would be to emphasize the magnitude of the number of GE mosquitoes released. For example, the EA could have stated instead that *they will temporarily increase the total mosquito population by at least 50 percent; that male mosquitoes can be an annoyance even though they do not bite; that thousands of biting GE females will be released in the target area during the trial; that even more than 2.4 biting per week GE females will exist in some households where mosquitoes might concentrate; and that all of these numbers are low estimates.* Thus, the way in which the conclusion is stated in the final EA represents a framing issue that violates the principle of reflexivity (specifically, the criterion requiring the examination of framing and the acknowledgment of alternative explanations), and alternative ways of interpreting the release of GE female mosquitoes could have been presented along with the original.

The estimate of the number of GE mosquitoes (female and male) released in the trial area is used in subsequent portions of the risk analysis to consider the potential adverse effects on humans and nontarget species. Key to an effects assessment is the consideration of survivability and spread of the GE mosquitoes over time, which is discussed next.

3.2.2. Survival

The molecular control switch that Oxitec has developed (for making the GE mosquito dependent on tetracycline for its survival) is not perfect. According to the draft and final EAs, upwards of 3.7–4.3 percent of the GE mosquito population (with OX513 tTAV genes) may survive in the absence of tetracycline (FDA 2016b, p. 55; Oxitec 2016, p. 53). If 5 percent of the second-generation progeny survives, with approximately half of that population being female (FDA 2016b, Appendix C) there will be a number of female-biters with the OX513A gene and there will be a significant number of potential egg layers to sustain the GE trait in third generations and beyond. Reeves *et al.* state that “OX513A males are only partially sterile, and when they mate with wild females, they will produce 2.8%–4.2% the normal number of eggs, half of which will be biting daughters” (Reeves 2012). Thus the GE mosquito may survive through this “leakiness” of the technology, but neither Oxitec nor the FDA tried to quantify this effect over time with risk assessment and population modeling to assess the survival of the GE mosquito with

several generations born in the wild. This gap seems to violate the principles of procedural validity (e.g. use of all relevant, available information and subjective probabilities) and anticipation (e.g. asking “what if?”) of PRRAF (Table 1). Population modeling over time under different best and worst-case scenarios, taking into account variability and uncertainty, would yield more useful information about the persistence of GE females and males in the environment and give more credence to the determinations of human and environmental risks.

An even greater percent of GE mosquitos would survive in the presence of tetracycline. The EA report assumes that tetracycline will not be present in significant amounts in the environment to affect their survival. This is a problematic assumption as there are potential sources of the antibiotic within or only meters away from the trial site (FDA 2016b, p. 55). Notably there is a hospital/clinic within 300 meters and a wastewater treatment plant in the field trial area itself, which the EA states: “could hypothetically hold waters with residues of tetracyclines” (FDA 2016b, p. 56). The EA argues that the hospital/clinic is removed from the trial area by a buffer of water and vegetation, and that the GE mosquitos would not transfer across it because of their limited mobility. With regard to wastewater treatment in the area, it states: “examination of tetracycline levels from wastewater treatment plants and their downstream flow (...) are expected to have particularly high levels,” notably in the microgram per liter ($\mu\text{g L}^{-1}$) range (FDA 2016b, p. 56). Looking at the tables of survivability of the GE mosquito in the EA (FDA 2016b, table 3, p. 55) and by their own conclusions, the assessment authors admit that significant effects in survivability of the GE mosquitos are seen over 1 ng mL^{-1} ($1 \mu\text{g L}^{-1}$) tetracycline, overlapping with the range of concentration that occurs in the flow from wastewater (FDA 2016b, p. 55, 2016c, Appendix C, p 5). However, the final EA makes two assumptions to support the conclusion that these levels will not impact the survivability of the GE mosquito at the trial site. First, tetracycline degrades in the environment in sunlight, and second, wastewater could not be a habitat for mosquitos around homes because “artificial containers such as used car tires, flower vases, water storage vessels, and discarded materials” (FDA 2016b, p. 56) are more typical breeding environments.

These are bold and unwarranted assumptions. First, tetracycline is routinely detected in the environment, as several studies that are cited in the final EA indicate. Although it degrades, there is continuous renewal of supply (or flow) into the environment from hospitals, wastewater, animal agriculture, and other sources. This seems to be simple logic that is ignored in the discussion in the final EA. Second, puddles of water contaminated by the wastewater treatment facility near homes could also be a habitat. It is also not obvious why the researchers did not go to homes in the trial area and collect standing water to test it for tetracycline. This would not have been too expensive, relatively speaking, as simple analytical chemistry tests could have been conducted between the early drafts of the EA and the final (FDA 2016b; Oxitec 2016). This omission in testing the trial area for tetracycline could engender suspicion in the eyes of the public, such as the perception that the company was hesitant to test the water in case it did find concentrations of tetracycline around or over $1 \mu\text{g L}^{-1}$.

Several principles of PRRAF are violated by this case. The principle of humility was violated in that the social and behavioral aspects of humans regarding water around their homes were not seriously examined using data collection and analysis. The principle of reflexivity was not respected in that the assumptions about degradation and the presence of tetracycline were one-sided, in favor of minimizing risk, and alternative explanations to the data and analysis were not presented. The principle of procedural validity was not met in that there was a lack of consistency in interpreting the cited and their own studies. Dagherir and Drogui (2013) state that tetracycline accumulates in living systems and in surface, ground, and wastewater. Given the lack of data and potential sources for tetracycline in the trial area, there could be some places where concentrations are high enough to repress the lethality gene, according to the literature and Oxitec’s own assessment (FDA 2016b, p. 56; Oxitec 2016, p. 53).

The three sources of leakage in the system – the continual release of under 0.2 percent GE females, imperfections in the molecular repressor system, and the possibility of significant tetracycline in the environment – suggest that GE mosquitos will indeed be present over time, and that their numbers, including females, might not be insignificant. There will be the 0.2 percent from each initial release (a couple of times a week), but also approximately 3 percent (if tetracycline is $1 \mu\text{g L}^{-1}$ and lower) and possibly more than 5 percent (if tetracycline is $1 \mu\text{g L}^{-1}$ or higher) in subsequent generations (FDA 2016b; Oxitec 2016).

Oxitec and the FDA have discounted that possibility without conducting population or risk modeling studies over time and accounting for variability and uncertainty. This is a serious flaw, violating the PRRAF principle of

anticipation of future consequences. Oxitec has or could collect enough data to do some basic risk modeling for the EA. Other modeling studies have shown significant spatial and temporal variability in the number of surviving, resistant, and persisting GE mosquitos with this sterility technology (Legros *et al.* 2016; Alphey & Bonsall 2017; Watkinson-Powell & Alphey 2017). Furthermore, if more voices had been included in the risk analysis process, those flaws could have been identified and remedied (PRRAF principle of inclusion). The FDA only consulted an interagency group for the EA and FONSI analyses with representatives from the EPA, the FDA, and the Centers for Disease Control, and the agency reports no other expert stakeholder consultation in the FONSI, aside from the rulemaking and comment process (FDA 2016c). There appears to be a one-sided interpretation of evidence (in favor of allowing release) that compromises the rigor of the risk analysis.

3.2.3. Spread

Spread depends on the interaction of survival time and ability to travel over geographic distance during that time, among other variables. Not only is the survival of the GE mosquito a serious possibility, but their spread in the environment is also a matter of concern. The EA, on the one hand, claims that because *Aedes aegypti* mosquitos live primarily in human-managed ecosystems (e.g. tires filled with water outside homes), it is unlikely to spread to national wildlife areas. But, on the other hand, the EA acknowledges that the species (albeit in very small numbers) has been found in national wildlife refuges in the Florida Keys where endangered animals live (Leal & Hribar 2010; FDA 2016b, p. 47; Oxitec 2016, p. 44). Minimizing the possibility that the mosquito and (presumably) its GE counterpart may be able to survive in ecosystems that are untainted by human presence, the EA claims, “[i]t is therefore concluded that release of OX513A will not affect threatened and endangered species or their habitats in Monroe County as there is *no habitat overlap* between the Key Haven release site and the habitat of these species” (Oxitec 2016, p. 45; FDA 2016b, p. 48). Although the effects of the spread of the GE mosquito may be minimal, the assessors again choose to downplay the possibility of spread in emphatic language in the EA that is at best misleading if taken out of context. The principle of reflexivity would require a more balanced summation of the data with assumptions examined through multiple interpretations and then reported with openness and transparency associated with procedural validity. Following the principle of anticipation would lead to a better examination of the scenarios (including the worst-case scenario) under which the GE mosquito could travel to protected and unmanaged ecosystems with endangered species.

The agency’s assessment of the probability of the spread of the GE mosquito in the environment is also laden with interpretations of evidence that ignore the social factors that shape risk and how those create vulnerabilities in ecosystems (Table 1). To consider these factors would constitute a humility-based approach associated with PRRAF. The FDA has claimed that “given that this trial would be carried out concurrently with the existing Florida Keys Mosquito Control District (FKMCD) integrated vector control program currently in place, it is unlikely that OX513A mosquitoes would disperse beyond the trial site” (FDA 2016c, p. 7). However, there is evidence that the *Ae.aegypti* “... can also be dispersed by human activities such as passive transport on boats, trains, automobiles, etc ...” (Gloria-Soria *et al.* 2014). In fact, Gloria-Soria *et al.* (2014) note that the species has been found (for the first time) in California and they believe that it came from the Southeastern US. Given that *Ae.aegypti* has travelled from Florida to California, it is reasonable to suppose that its genetically engineered counterpart may be capable of doing the same under existing FKMCD control programs. Therefore it is confounding that the FDA reported in the FONSI statements that the travel of the GE mosquito OX513A strain outside the trial area is “unlikely” (FDA 2016a, 2016c, p. 7) when the OX513A strain survives in the environment at a certain percentage and the species has traveled outside the area before. However, the FDA discounts this possibility, and then goes on to conclude that because exposure to the GE mosquito is unlikely, all of the risks associated with this exposure are negligible.

Furthermore, in the draft EA, the agency stated:

... [t]he population of *Ae. 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 Ae aegypti from areas that did not receive OX513A male mosquitoes.* (Oxitec 2016)

In the final EA, it states (not giving a reason this time) that “the wild-type *Ae. aegypti* population would be expected to recover to pre-trial numbers after the cessation of OX513A mosquito releases” (FDA 2016b, p. 5).

Apparently, if the FDA's FONSI are to be believed, *Aedes aegypti* mosquitos can only travel in one direction (into the trial site but not out of it).

Our larger point is that the agency's assessment errs by not considering the very real possibility of failure and not appropriately acknowledging the significant role of human activities in the spread of the GE mosquito, thus minimizing the exposure or pathway components of risk. The FDA's FONSI endorsed conclusions that are inconsistent with the evidence, did not consider scenarios of what might happen under different conditions and over time, and failed to consider alternative explanations and assumptions. Thus, their analysis does not meet PRRAP's principles of procedural validity, humility, or anticipation.

3.3. PPRAF evaluation of risk characterization

Risk characterization brings together the consideration of the likelihood and pathways of occurrence or exposure with the severity or magnitude of the adverse effects and summarizes that integration in written or graphic form. We present an example of risk characterization that is dependent on survival over time, and then the general, overall process that FDA and Oxitec use to characterize risk in its reports is examined.

A significant risk of increased disease transmission could arise if there were simply more *A. aegypti* mosquitos in the environment to transmit viral vectors, such as Zika and Dengue. The potential increase in human disease risk from continual releases of the GE mosquito over two years of the trial is characterized in the EA and FONSI by considering the risk pathways dependent on survivability. In doing so, the FDA states in its FONSI conclusions:

OX513A male mosquitoes *do not bite* and, consequently, do not transmit diseases. A small number of females may be co-released with OX513A male mosquitoes or be present at the site of the proposed release as a result of incomplete penetrance of the introduced lethality trait. However, there is no evidence to suggest that OX513A females are fitter or more competent vectors than wild-type *Aedes aegypti*. *In fact, evidence suggests OX513A females have decreased vector competence because any OX513A females are expected to die in 2–3 days time, as the lack of tetracycline in the environment will turn on the lethality trait resulting in a lifespan too short to vector viral disease.* The lifespan of OX513A females is shorter than the external incubation period, (EIP) for arboviruses such as dengue and Zika thereby disabling virus transmission to a human host at a subsequent blood feeding ... the EIP for dengue is estimated at 10–14 days ... Therefore, FDA concludes that the likelihood of adverse effects associated with an increase in transmission of dengue or other diseases transmitted by OX513A mosquitoes is extremely low and the risk is negligible. (FDA 2016c, p. 4)

This conclusion is problematic in the face of evidence and data presented in the EA. First, there will be a certain (perhaps low, but not zero) percentage of biting female GE mosquitos in the environment that cannot be estimated from the risk assessment over time because of the lack of models, and there will be variability associated with this number depending on a variety of factors, including the concentrations of tetracycline in the environment. Second the statement that “females are expected to die in 2–3 days” flies in the face of data presented in the draft and final EAs. The final EA shows graphically how GE mosquitos (both female and male) survive for much longer than 2–3 days, even in the absence of tetracycline (i.e. the 5 percent or so that will emerge as a result of the leakiness in the molecular system) (FDA 2016b, Fig. 3, Appendix F). In fact, the final EA states: “A small fraction (about 20%) survived long enough to take two blood meals (that is over 20 days)” (FDA 2016b). It is a matter of interpretation as to whether 20 percent is a small fraction, but surviving 20 days is enough time to incubate the Dengue virus, as stated in the FONSI. In fact, when one examines the data in the EA, approximately 10 percent live 40 days or more and 5 percent live 50 days or more (FDA 2016b, Fig. 3, Appendix F). From this example, it is quite clear that uncertainty and variability are downplayed in the final risk characterization of increased human disease transmission. This violates reflexivity in not examining assumptions and considering alternative explanations (in the final risk estimate) and procedural validity in inconsistent data interpretations and lack of openness and transparency in the FONSI language (compared to the EA).

Qualitative rankings are employed for all of the risks considered in the final EA, such as in the quote above: for example, “extremely unlikely” is used to describe the exposure or risk pathway and “negligible” the final risk. The draft EA report also employs a qualitative risk assessment method that was taken from the Australian Office

of the Gene Technology Regulator, the regulatory agency for GEOs in Australia (Oxitec 2016, Table 9). This approach first describes the pathway to harm, then uses linguistic terms to combine “likelihood” and “consequence” to estimate “risk” (Oxitec 2016, p. 102). Likelihoods are evaluated as “highly unlikely” to “highly likely” and consequences as “marginal” to “major” (Oxitec 2016, Table 8). There are flaws to this approach in the draft EA, but at least one can identify and scrutinize those flaws. For example one flaw is that Oxitec rates various risks from the GE mosquito as “negligible” even though they vary in the magnitude of their consequences or likelihood. According to the EA, the same likelihood with different levels of consequence (minor vs. marginal) may have the same risk estimate. This error in risk estimation could have been avoided by either conducting a probabilistic risk assessment or by assigning numerical rankings (1–4) for each category (likelihood and consequence) and adding them to reach a more precise estimate of their risk. In the draft EA, Oxitec also evaluates uncertainty qualitatively rather than quantitatively, which creates inconsistency in the description of what is known and what is not known. For example, Oxitec’s draft EA report states:

The potential likelihood (of OX513A) to establish 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, p. 118)

But then the draft report concludes that there is a “high degree of certainty that the OX513A is unlikely to establish in the environment” (Oxitec 2016, p. 118). It is unclear on what grounds Oxitec can simultaneously assert that the potential for establishment is of “medium confidence of uncertainty” and a “high degree of certainty.” The FDA did not question the discrepancy in Oxitec’s statements.

Unfortunately, this qualitative method of risk ranking did not improve in the final EA risk assessment, and in fact became more obscure and inaccurate according to common definitions of risk. First, in the final EA, there is no table like Table 8 (Oxitec 2016) in the draft EA, which describes the scale for rating each standard dimension of risk (i.e. likelihood and consequence). In the draft EA, at least a published methodology of GE mosquito risk assessment with a defined qualitative risk ranking from the Australian gene regulator was used. The final EA changes the language of the risk rating in Table 9 (FDA 2016b), without citing a source for the method. Second, in comparison to the draft EA, the final EA again contains the problem that different qualitative values in one component of two dimensions (in the case of the final EA both likelihoods, without magnitude of consequences) lead to the same risk ranking. For example, all of the “likelihoods of adverse effects” are rated as extremely low (EL), and although there is minimal variation in the “likelihood of exposure” from “highly unlikely” (HUL) to “unlikely” (UL) *all* of the risks are ranked as negligible (either HULxEL or ULxEL, both resulting in “negligible” risk). One cannot ascertain if the final risk estimate included possibilities other than “negligible,” as they are not shown. Additionally, they are not defined quantitatively; for example, is HUL a one in a million chance or a one in a thousand? This presents additional procedural validity problems of inconsistency in how the assessment prescribes qualitative terms to the categories.

Third and most importantly, in the final EA, both dimensions of risks are likelihoods, which is inconsistent with the definition of risk articulated by well-respected risk assessment bodies. The final EA incorrectly categorizes what a risk is; instead of considering the pathway (likelihood) and severity of adverse effects of that pathway (severity of consequences), it stops at earlier and intermediate points in pathways of exposure, events or effects, calling them “risks.” Instead of ranking the severity of consequences and combining them with the likelihood of exposure, it combines two likelihood parameters: “likelihood of exposure” with “likelihood of adverse effects,” never estimating the *severity of adverse effects*. Thus, there is not only a lack of transparency in the scale that the final EA uses for the two likelihood estimates, but also there is no estimation of the severity of the consequences in contrast to the draft EA (FDA 2016b; Oxitec 2016). In contrast to the draft EA, the final EA also omits any ranking of uncertainty, which at least gave us an indication of how confident the researchers were in the assumptions and estimates (FDA 2016b; Oxitec 2016). It appears as if the final EA is hesitant to evaluate a major component of risk assessment (severity of consequences) given that this is a place of greater uncertainty in the release of GE mosquitos. In other words, it is easier to collect data on *whether* the mosquito might come into contact with wildlife, but much harder to obtain information about the severity of the consequences if it *does* come into

contact with wildlife (e.g. would the population decline, and if so, by how much?). This approach violates the principles of procedural validity and reflexivity in the sense that there is a lack of consideration of the validity, assumptions, and acceptability of the approach.

Ignoring severity comes from faulty assumptions about risk assessment. For example, in estimating risk in the final EA, the document states: “there must be both exposure and an adverse effect to pose a risk” (FDA 2016b, p. 113). This is true. But the EA takes it a step too far stating in the draft FONSI that: “[b]ecause risk is a function of hazard and exposure, if exposures are negligible, risk will also be negligible” (FDA 2016a). This is not true, as a very low (even negligible, non-zero) dose of a very toxic substance can pose a high risk. The FDA’s argument ignores the logic of risk assessment and years of risk assessment scholarship. Consider that even low (or negligible) levels of very toxic compounds, like the botulinum toxin family (LD_{50} s about 5 ng kg^{-1}), can lead to greater risk than the same level of exposure to other less toxic compounds. The FDA’s risk analysis disregards approaches used for low probability yet high consequence events, such as fault tree analysis (e.g. that is used for nuclear power accidents, which can have severe impacts). In contrast, an Australian group of researchers associated with Commonwealth Scientific and Industrial Research Organisation (CSIRO) modeled their risk assessment of a mosquito modified with bacteria and its population suppression ability using a fault tree analysis that considered multiple pathways of failure and endpoints for human and ecological health, social impacts, and economic effects (Murphy *et al.* 2010).

In summary, in keeping with the PRRAF’s principles of inclusion and humility, Oxitec and the FDA should have consulted with outside experts, stakeholders, and citizens with specialized and local knowledge (NRC 1996) to assign ratings to the likelihood of exposure and the severity of consequences/effects. They should have been more transparent and open in the final EA as to the choices of the rankings in the two likelihood components that are used for “risk.” They should have discussed the assumptions and limitations of their approach and why an estimation of the second major component of risk (severity or magnitude of the consequences) was not made. The procedural validity of the risk assessment conducted by Oxitec and the FDA would have been higher if they had taken these steps, and also if they had incorporated subjective probabilities from multiple experts and provided opportunities for reflection and learning to the company, the FDA, and the public. Furthermore, there is no reflexivity in the risk assessment as a discussion of limitations to methods, processes, and assumptions in estimating “risk” are absent.

4. Discussion

The FDA’s risk assessment protocol for GE animals falls short not only in standard methods of risk assessment such as consistent interpretation of uncertainty and appropriate use of data in characterizing risk, but also in multiple ways when evaluated according to the principles of the PRRAF (Table 1). It does not appropriately evaluate environmental risk using the best available methods and data. For example, the decisions made by the FDA and Oxitec to forgo quantitative risk assessment, not to estimate probabilities from data in the EA, not to employ outside experts in the “weight of evidence,” and not to use Bayesian expert elicitation approaches constitute a methodology that has multiple flaws. Such an approach violates PRRAF’s principle of procedural validity. Moreover, it uses fuzzy language that results in key assumptions being obscured from scrutiny. The FDA’s risk analyses could have benefited from more humility-based and inclusive approaches for qualitative risk assessment rankings. The two EAs and FONSI show a lack of rigor and a systematic interpretation of uncertainty or variability in data in favor of adoption of the new GEO. That bias is ethically and politically significant and may affect the legitimacy and acceptability of the agency’s risk assessment in the eyes of the public.

In this article, PRRAF is used to evaluate a case study of regulatory risk assessment of GEOs based on the author’s own judgment in consultation with colleagues. Ideally in governance more voices would judge whether a risk assessment process meets PRRAF criteria and principles. For example, PRRAF could be used by an independent, external advisory group to evaluate the procedural and substantive validity of risk analyses used for regulatory decisionmaking. Diverse group members coming from different disciplines, viewpoints, organizations, and parts of the socio-ecological system into which the GEO is being deployed could rate the conduct of risk assessment according to the criteria and principles of PRRAF (Fig. 1). As suggested by NASEM (2017), it is especially important to open up the regulatory process to advisory committees and stakeholders when emerging products

of biotechnology are complex and unfamiliar. Gene drives would fit these conditions. There have also been strong recommendations to engage residents in geographic areas where gene drives are to be deployed so that they may be informed, have input, or even give consent (e.g. NASEM 2016; Koefler *et al.* 2018). Communities in areas of GEO release could use PPRAF to evaluate the process of risk assessment. PPRAF can help to make choices about what risk models or data to use through more legitimate and rigorous engagement with external communities to examine assumptions, reflect, frame problems, and get feedback at key junctures in the risk assessment. At a minimum, under conditions of low capacity for external engagement, PPRAF should be used by those conducting risk assessments to reflect on their own processes as part of responsible development of GEOs and gene drives (Fig. 1).

It is likely that the FDA will continue to have authority for GE animals, and it will regulate some GE animals and insects with gene drives (White House 2015, 2017a, 2017b; FDA 2017b). As an interim step to adopting PPRAF, the FDA could model its risk assessment on the risk evaluation conducted by the CSIRO, which followed several of the principles of PPRAF (Murphy *et al.* 2010; Murray *et al.* 2016). The CSIRO conducted risk analysis of the release of genetically modified mosquitos for disease suppression that included diverse experts and stakeholders in the framing and conduct of the analysis (inclusion), considered the social and behavioral foundations of vulnerability (humility), compared the risks of the modified mosquitos to non-technological options (humility), used subjective probabilities (procedural validity), and its report explicitly acknowledged the uncertainties in estimating probabilities of adverse events in the future (procedural validity and anticipation) (Murphy *et al.* 2010; Murray *et al.* 2016). The CSIRO assessment engaged interested and affected parties to develop fault trees and influence diagrams for a broad range of economic, social, cultural, ecological, and human health harms to estimate the probabilities of those harms (Kolopack *et al.* 2015).

The FDA's review protocol raises concerns about the ability of the agency to effectively regulate existing GE animals under its purview, as well as anticipated future ones, such as those with gene drives. Given the potential of gene drive systems to permanently alter the composition or eradicate wild populations, it is crucial that the FDA's risk assessment process is strengthened before the agency has to make a regulatory decision about organisms with gene drive systems. Under these circumstances, regulatory decisionmaking should be informed by a commitment to humility and the other four principles of PPRAF.

US oversight systems may currently lack the capacity in staffing and resources to conduct analyses according to PPRAF principles for every GEO that is regulated by federal agencies (NASEM 2017). However, releases of the first GE insect (like OX513A) for disease control, as well as animals with gene drives, entail situations of high complexity, uncertainty, and novelty and therefore warrant such an approach. Recent reports released by the IRGC (2015) and NASEM (2016, 2017) also recommend engaging a wider range of experts, stakeholders, and publics under these conditions. PPRAF provides a flexible yet robust framework to guide more engaged approaches to risk assessment and decisionmaking about emerging GEOs. It could complement a variety of regulatory and legal contexts as agencies move forward with their new strategic plan for overseeing GEOs (White House 2017b). The PPRAF can also be used by other nations and international organizations facing the challenge of regulating GE insects and animals, including organisms with gene drives.

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Notes

1 See discussion of similar risk endpoints for new and old methods of genetic engineering in NASEM 2017.

- 2 These arguments are not detailed in this analysis, but rather used as a starting point in developing PRRAF. PRRAF establishes the standard that risk assessors should engage in critical dialogue with public constituencies (such as outside experts, stakeholders, interested and affected parties, and communities in proximity to their release, as suggested in NASEM 2016, 2017 reports; NRC 1996) to determine the normative considerations that shape their work, as well as to reflect on the validity of the procedures, assumptions, and methods used.
- 3 Note that the third criterion overlaps with one under the principle of inclusion for involving interested and affected parties in problem framing in risk assessment, but it is also included under the humility principle to emphasize a broader sense of eliciting public input into options that might not be included in the risk assessment at all but that could involve the comparison with other technological or non-technological options.
- 4 Note that the local decisions and political processes that occurred in Florida, such as the public communication efforts that Oxitec and the local mosquito control board undertook, or the local mosquito board's decision to comply with the public referendum, are not discussed in this article. These indicate forms of citizen inclusion in the broader political decisionmaking process that are beyond the scope of this paper, as they do not relate specifically to the risk assessment process. Instead, this analysis focuses on the process of the risk analysis for formal regulatory approval from federal agencies. Risk analysis under FDA regulatory review is to date the key decisionmaking step for US federal oversight of GE animals (insects in this case).

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