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Prescribing engagement in environmental risk assessment for gene drive technology

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Abstract

Gene drive technology is a nascent biotechnology with potential to purposefully alter or eliminate a species. There have been broad calls for engagement to inform gene drive governance. Over the past seven years, the gene drive community has been developing risk assessment guidelines to determine what form future gene drive risk assessments take, including whether and how they involve engagement. To explore who is developing these guidelines and how engagement in risk assessment is being prescribed, we conduct a document analysis of gene drive risk assessment guideline documents from 2014 to 2020. We found that a narrow set of organizations have developed ten key guideline documents and that with only one exception the documents prescribe a narrow, vague, or completely absent role for engagement in gene drive risk assessment. Without substantively prescribed engagement in guidelines, the relevance, rigor, and trustworthiness of gene drive risk assessment and governance will suffer.

Key words

Engagement; Environmental risk assessment; Gene drive technology; Participation; Risk assessment guidelines

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1. Introduction

Gene drive technology is a nascent biotechnology with potential to purposefully alter or eliminate an entire species through biasing inheritance. Researchers are developing applications primarily for insects and rodents to eliminate or suppress problematic populations. The potential benefits of gene drive technology may be significant in global health (e.g., to eliminate or suppress mosquitoes for malaria control), agriculture (e.g., to eliminate or suppress the invasive spotted wing drosophila fruit fly) and conservation (e.g., to eliminate or suppress invasive mice on islands). Research continues and developers have not yet released gene drive organisms into the environment, but they expect the first field trials of gene drive mosquitoes for malaria control in the near future in sub-Saharan Africa (Scudellari, 2019; Naegeli et al., 2020). The novelty and power of gene drive technology, including the potential to eliminate or alter entire species has highlighted the importance of both risk assessment and engagement in gene drive technology governance (NASEM, 2016). Regulators, developers, non-governmental organizations, academics, and a host of other stakeholders are all considering and debating what form gene drive-related risk assessment and engagement should take (Devos et al., 2021; Dressel, 2019; Gordon et al., 2021; Hartley et al., 2021; Hoffman et al., 2017; Kuzma, 2019; Naegeli et al., 2020).

Environmental risk assessment (ERA) is a process to synthesize science to inform decision making, or more formally to: "systematically evaluate and organize data, information, assumptions, and uncertainties in order to help understand and predict the relationships between stressors and ecological effects in a way that is useful for environmental decision making" (US EPA, 1998). ERA classically has three steps: problem formulation, analysis, and risk characterization. Problem formulation is where many of the foundational decisions for the risk assessment are made, including selecting the potential stressors, valued ecological entities, and potential adverse effects that will be assessed, as well as determining the analysis plan for the remainder of the risk assessment. The analysis step looks at whether the stressor will impact the valued entity, and if so, the likelihood and severity of any resulting adverse effects. Finally the risk characterization step summarizes the findings for the decision context. ERA can involve

synthesizing existing studies or conducting additional studies – all decisions that are generally made in the problem formulation step. Risk assessment is privileged in governance decisions at the national and international level, with organizations such as the European Food Safety Authority, the United States Environmental Protection Agency, and the Convention on Biological Diversity all calling for risk assessment to inform decision making around gene editing (Convention on Biological Diversity, 2018; EFSA Panel on Genetically Modified Organisms (GMO), 2013; US EPA [online], 2021). The establishment of ERA processes in advance of gene drive field trials is essential and therefore it is currently receiving heightened attention.

In addition to the attention paid to risk assessment, there has also been broad recognition of the importance of engagement in governance decisions surrounding gene drive technology (Adelman et al., 2017; Ledingham & Hartley, 2021). Engagement is important because the governance decisions facing these technologies are normative or values-laden and should not be in the hands of a few experts but should be open to inclusive societal deliberation (Sarewitz, 2015). Engagement is justified on a variety of grounds including: *normative*, underpinned by democratic values and the recognition that people have a right to influence decisions that will impact them; *substantive*, on the basis that different actors will bring valuable knowledge to improve governance decisions; and *instrumental*, to build trust and legitimacy, and minimize conflict (IRGC, 2017; Webler & Tuler, 2018).

At the intersection of the previous discussions about ERA and engagement is the importance of engagement in ERA itself. This is based on the realization that the normative or values-laden nature of gene drive governance decisions extends into risk assessment. That is, ERA contains a host of decisions that one may make differently depending on one's expertise and worldview (Jensen et al., 2003; Thompson, 2003). Such decisions include, for example: What are the most important components of an ecosystem to protect? What counts as harm vs. inconsequential change to a component of the ecosystem? When are additional studies needed? What level of certainty is adequate for characterizing a risk? Given the importance of these foundational questions to the ERA process, many scholars have prescribed a role for engagement in ERA,

including in biotechnology-related ERA (Dana et al., 2012; Hartley & Kokotovich, 2018; Kokotovich et al., 2020; Kuzma, 2019). This scholarship calls for using deliberative methods to include individuals with a diversity of expertise and worldviews within the ERA process. Such engagement seeks to open the "black box" of risk assessment to help identify consequential decisions and explore what is at stake in how they are made – that is, using inclusion and reflexivity to improve risk assessment. While these prescriptions for engagement in risk assessment have been made in different forms for decades, there has been less success in actually incorporating engagement within risk assessment processes than in other decision-making spaces. The engagement that has taken place has been largely and narrowly within the problem formulation phase (i.e., James et al. 2018).

Another important component of the gene drive ERA picture is the role of risk assessment guidelines – the "cookbook" that lays out how to conduct a risk assessments and what should be included in it. Risk assessment guidelines delimit the scope of future risk assessments by determining, for example, the general topics in need of addressing, the type of evidence required, and, importantly, what role engagement should play in risk assessment. Codex Alimentarius Commission ('Codex') defines risk assessment guidelines as the 'documented guidelines on the choice of options and associated judgments for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process in maintained' (CAC, 2013: 114). Many argue that guidelines, themselves, should be developed through inclusive processes involving stakeholders and other interested parties (Hartley & Kokotovich, 2018; Millstone, 2009). The recognition that risk assessment guidelines involve value choices strengthens the rationale for engagement in risk assessment (Elliott, 2019; Hartley, 2016). This recognition is shared by state actors, including the European Commission's Scientific Committees, the European Food Safety Authority (EFSA), and US regulatory agencies, who have reimagined non-technical actors as potential participants in the development of risk assessment guidelines (Hartley & Millar, 2014; SCHER et al., 2013). However, in practice, risk assessment guideline development may be seen as a technical rather than a policy process that is led by risk assessors thereby reducing the opportunity for engagement (Hartley, 2016).

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Gene drive ERA guidelines are currently being developed for gene drive technology. These guidelines are highly consequential as they will help determine not only what steps will be followed to assess risks from this novel, powerful new technology, but also what form engagement will take in such risk assessments. This process of guideline development is not a formal one organized by a regulatory agency, but an informal process informed by a variety of groups convening workshops and working groups to develop documents describing how gene drive ERA should be conducted. These guidance documents are forming the basis for an international consensus on what form risk assessments for gene drive technology need to take. Given their consequential nature, we examine these emerging gene drive ERA guideline documents in order to understand how engagement for future gene drive ERA is being prescribed. Gene editing-enabled gene drive technology began less than a decade ago and documents evidencing the unfolding process of risk assessment guideline development can be traced to 2014, so there is a clear and concise documentary dataset for analysis. This study is timely because while the gene drive community, which includes the technology developers, funders, supporters and other stakeholders, have demonstrated and articulated a desire for stakeholder and public engagement in the technology's development (Hartley et al., 2019; NASEM, 2016) including in risk assessment (Devos et al., 2021; Long et al., 2021), it is unclear whether these intentions are finding their way into discussions about ERA and ERA guidance documents.

Through document analysis, we found that between 2014 and 2020, ten key guideline documents articulated what form gene drive risk assessment should take going forward including what role there should be for engagement. The majority of these documents (seven) either do not mention engagement in risk assessment or make vague calls for engagement in risk assessment. Only one of the ten documents prescribes the role of engagement in gene drive risk assessment in a detailed, thorough, and substantive way. In addition, the meetings or working groups that lead to these documents were convened by a relatively narrow set of actors based in the US and Europe. These findings are problematic for ERA and for risk governance more broadly, given the likely importance of ERA in future decisions on whether and how to use gene drive technology. The

judgments present within ERA guidelines and product specific ERAs delimit whether and how certain potential adverse effects from gene drive technology are studied. If actors with relevant knowledge, including local stakeholders, do not inform these guidelines and specific ERAs, the characterized risks may not be adequately relevant, rigorous, or trusted. More generally, our findings reveal the paucity of imagination about what engagement in ERA might look like and point to the need for further empirical and theoretical attention on the types and timing of engagement needed in both guidelines and for the individual case-by-case risk assessments for emerging biotechnologies.

2. Methods

We conducted a document analysis of gene drive risk assessment guidance documents from when they first emerged (2014) until January 2020. We included in our data set documents that: 1] constitute guidance specifically relating to gene drive risk assessment; and 2] result from an interdisciplinary workshop or working group. To constitute guidance, documents had to do more than just call for risk assessment – they had to describe in detail what form gene drive risk assessments should take. We focused on guidance from interdisciplinary workshops and working groups because these large collaborations often hold greater authority than individual authored pieces and they represent, themselves, efforts at inclusiveness. Documents in our sample included reports and academic articles.

Our search terms yielded ten documents, which we analyze in Section 3. We also found a variety of documents related to gene drive risk assessment that ultimately fell outside of our search criteria. One group of such documents involved reports from workshops that broadly explored gene drive governance but did not address risk assessment in enough detail to constitute guidelines. For example, Farooque et al. (2019) and Australian Academy of Science (2017) were reports from a workshop and working group, respectively, that explored a host of governance issues surrounding gene drive technology. While risk-related issues were discussed in these reports, there was not a detailed, substantive discussion of what form gene drive risk assessment should take, and thus they do not constitute risk assessment guidance. Another group of

documents that fell outside our search criteria involved gene drive risk assessment guidance that emerged from individual academics and not interdisciplinary workshops or working groups (e.g., Kuzma 2019).

Document analysis is a well-established qualitative research method (Bryman, 1989; Shaw et al., 2004). The documents analyzed herein are all publicly accessible and self-identify their contributing organizations and authors. Thus, many ethical issues which regularly constrain social research such as privacy, confidentiality and so on, were negated (Hodder, 1994). As a research team we met monthly for 12 months to guide the analytical and writing process. These regular meetings were a core aspect of the methodological process and ensured a crucial unity of vision and understanding. The analytical process included an iterative process of defining inclusion criteria, identifying potential documents and their discussions of risk assessment and engagement, and discursively analyzing how engagement in risk assessment was envisioned in these documents. In the analysis of how engagement in risk assessment was prescribed, we focused on: What parts of risk assessment is engagement suggested for? What level of detail is provided in the discussion of what form engagement should take? To what degree are issues concerning engagement process and challenges discussed?

3. Gene drive risk assessment guidelines and engagement

This section describes and analyzes the ten gene drive risk assessment guideline documents created from 2014 to 2020 that we found in our search (Table 1). Our analysis of these documents revealed that they prescribed engagement in risk assessment in three general ways: 1) Two documents did not prescribe engagement in risk assessment (Section 3.1); 2) Five documents vaguely prescribed engagement in risk assessment (Section 3.2); and 3) Three documents substantively prescribed engagement in risk assessment (Section 3.3). The documents that vaguely prescribe engagement in risk assessment largely point to the need for engagement but offer no substantive discussion of how to achieve this or what it looks like, while the documents that substantively prescribe engagement in risk assessment discuss in detail what form such engagement should take and what issues face such engagement.

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Table 1: Guidance documents for gene drive ERA and the degree to which they prescribe engagement

Document number, title, citation, and description	Convener	Engagement in ERA
2014		
D1: *Guidance framework for testing of genetically modified mosquitoes* (WHO/TDR & FNIH, 2014) **Guidance framework for testing and regulating gene drive and other new genetic technologies.**	WHO/TDR FNIH	Not prescribed
2016		
D2: *Gene drives on the horizon: advancing science, navigating uncertainty and aligning research with public values* (NASEM, 2016) **In-depth report on the science, implications and governance of gene drives.**	NASEM	Vaguely prescribed
2017		
D3: *Results from the workshop "Problem formulation for the use of gene drive in mosquitoes"* (Roberts et al., 2017) **Journal article from FNIH workshop in 2016.**	FNIH	Vaguely prescribed
2018		
D4: *Risk assessment method for activities involving organisms with a gene drive under contained use.* (van der Vlugt, van den Akker, et al., 2018). **Report outlining findings from a workshop and working group of risk assessors from the Netherlands, Belgium, Germany, and the UK to investigate a risk assessment approach for gene drive technology.**	NL National Institute for Public Health and the Env.	Not prescribed
D5: *Identifying and detecting potentially adverse ecological outcomes associated with the release of gene-drive modified organisms* (Hayes et al., 2018) **Journal article resulting from 2016 NCSU convened interdisciplinary workshop "A roadmap to gene drives: a deliberative workshop to develop frameworks for research and governance".**	NCSU	Substantively prescribed
D6: *Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: recommendations of a scientific working group* (James et al., 2018) **Journal article details recommendations of a multi-disciplinary working group based on consideration of the WHO Guidance Framework (D1) using a case study scenario based on reducing malaria transmission by *Anopheles gambiae* gene drive mosquitoes.**	FNIH	Vaguely prescribed
D7: Towards inclusive social appraisal: risk, participation and democracy in governance of synthetic biology (Stirling et al., 2018) **Journal article reporting on the 2016 NCSU, OECD, and CSIRO convened interdisciplinary workshop "Environmental release of engineered pests: building an international governance framework" which resulted in a journal special issue.**	NCSU CSIRO OECD	Substantively prescribed
2019		
D8: *Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018* (Teem et al., 2019) **Journal article from 4 African Regional Workshops held 2016-2018**	FNIH NEPAD	Vaguely prescribed

D9: *Study on risk assessment application of annex I of decision CP 9/13 to living modified organisms containing engineered gene drives* (Smets & Rüdelsheim, 2019) **Report on risk assessment under the Cartagena Protocol on Biosafety**	CBD	Vaguely prescribed
2020		
D10: *Evaluation of existing EFSA guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified insects with synthetically engineered gene drives* (Naegeli et al., 2020) **Draft report culminating from a variety of EFSA-sponsored meetings.**	EFSA	Substantively prescribed

3.1. Guidelines that do not prescribe engagement in risk assessment

In 2014, the World Health Organization (WHO), Foundation for the National Institutes of Health (FNIH) and Special Programme for Research and Training in Tropical Diseases (TDR) published their *Guidance framework for testing of genetically modified mosquitoes* (D1: WHO/TDR & FNIH, 2014). Over 40 experts contributed to this report across its various stages of development. This Guidance responded to a perceived need for standards and guidance on the design, testing and possible implementation of new vector control methods, including gene drive technology. It has become a well-cited document laying the groundwork for gene drive risk assessment, and was intended to "foster quality and consistency in the processes for testing and regulating" new genetic technologies (p. xv). While engagement is discussed and risk assessment is explored at length, discussions of risk assessment and engagement take place separately in this document and the potential role of engagement in risk assessment is never addressed. For example, engagement is discussed with regards to broader governance issues like informed consent and communication of risks, but not in the actually assessment of those risks.

In 2018, Van der Vlugt et al. (2018, D4) published a report, *Risk assessment method for activities involving organisms with a gene drive under contained use*, outlining the findings from a working group convened by the Dutch National Institute for Public Health and the Environment. This working group brought together risk assessors from the Netherlands, Belgium, Germany and the UK to investigate risk assessment methods for gene drive technology. While different aspects of gene drive risk assessment were explored at length, neither their resulting report (van

der Vlugt, van den Akker, et al., 2018) nor accompanying journal article (van der Vlugt, Brown, et al., 2018) mention engagement.

3.2. Guidelines that vaguely prescribe engagement in risk assessment

Our search yielded five documents (D2, D3, D6, D8, D9) that prescribe a role for engagement in risk assessment but only in vague ways (Table 2). While these documents indicate the need for engagement in risk assessment, they fail to consider what engagement would look like or how to achieve it. The implications of these vague prescriptions of engagement in risk assessment are further discussed in Section 4.

One example of a document in this category is the report *Gene drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values* (NASEM, 2016, D2), which resulted from a major effort exploring gene drive governance convened by the US National Academy of Sciences, Engineering, and Medicine (NASEM). This report is an in-depth interdisciplinary investigation on the state of science, implications and governance of gene drive technology and is well-recognized for its thorough review of governance issues in addition to the promotion of public and stakeholder engagement in gene drive governance. The interdisciplinary committee that drafted the report had 16 members from research centers and academic institutions, including 14 US-based experts, one Kenyan-based expert, and one UK-based expert.

While this report discusses both risk assessment and engagement at length, it largely considers them in isolation, with only vague calls for engagement in risk assessment. For example, Chapter 6 is concerned with risk assessment and notes the importance of cultural values being "reflected in regulations" and that risk assessment should incorporate "the concerns of relevant publics"(p.113, 128). The chapter implies engagement with vague assertions of needing to determine "the valued components of the ecosystem in question" and their "relevance to human interests"(p.119). However, despite these prescriptions, there is no mention of engagement in risk assessment or suggestion about how such 'value components' would be determined. Chapter 7 on 'Engaging Communities, Stakeholders, Publics' looks at the issue of engagement in detail, and makes only one passing indication that engagement should be considered in risk assessment.

Despite this lack of focus on engagement in risk assessment, the chapter ends with a recommendation: "Because engagement can contribute to defining the values and preferences of communities, stakeholders, and publics about gene drive technologies, researchers and risk assessors should integrate engagement into the construction of risk assessment models" (p.142). The concluding chapter makes the recommendation that, "Governing authorities, including research institutions, funders, and regulators, should develop and maintain clear policies and mechanisms for how public engagement will factor into research, ecological risk assessments, and public policy decisions about gene drives. Defined mechanisms and avenues for such engagement should be built into the risk assessment and decision-making processes from the beginning."(p.178). The report does not describe what form this engagement in risk assessment should take, what steps are involved, what challenges exist, or what specific methods that could be used. However, in even mentioning the potential role of engagement in gene risk assessment at all, it represents the first risk assessment guidelines document to do so. The NASEM report is progressive in its incorporation of discussions of risk assessment *and* engagement yet these discussions remain substantively isolated from one another.

Table 2. Illustrative quotes demonstrating the prescription of engagement in risk assessment that included no substantive discussion of engagement in gene drive risk assessment

D2: *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty and Aligning Research with Public Values* (NASEM, 2016) **"Because engagement can contribute to defining the values and preferences of communities, stakeholders, and publics about gene drive technologies, researchers and risk assessors should integrate engagement into the construction of risk assessment models." (p. 142).** **"Defined mechanisms and avenues for such engagement should be built into the risk assessment and decision-making processes from the beginning" (p.178).**
D3: *Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes"* (Roberts et al., 2017) **"It is also important to consider that there may be different perspectives on environmental protection goals… The authors would encourage these considerations to be taken up in appropriate forums, and particularly in communities where the use of gene-drive technologies would likely occur." (p. 533)**
D6: *Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: Recommendations of a scientific working group* (James et al., 2018) **"Thus, there will need to be a plan for how public input on hazards is solicited and integrated. Principles for both environmental and social impact assessment have been proposed." (p. 8)**
D8: *Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018* (Teem et al., 2019)

"Prior to the release of any such technology, it is important to hold conversations to help define the areas of concern that will likely need to be addressed in those risk assessments." (p. 11)
D9: *Study on Risk Assessment Application of annex I of decision CP 9/13 to living modified organisms containing engineered gene drives* (Smets & Rüdelsheim, 2019) **"These technical and methodological challenges will likely render the risk assessment for engineered gene drive applications more detailed and more complex, also requiring public consultation." (p. 6)**

James et al. (2018, D6) describes the outcomes from a FNIH-convened multidisciplinary scientific working group that explored what pathway should be followed to go from laboratory studies to large-scale open use for gene drive technology to address malaria causing mosquitoes. A variety of risk assessment-related topics were taken up by this working group. This working group developed recommendations over three multidisciplinary workshops and involved experts from academia, research institutes, government agencies, and nongovernmental organizations. There were 45 participants total across: 1) core working group members who participated in all working group activities and authored the recommendations (12 total: 4 Africa-based, 4 UK-based, 3 US-based, 1 Canada-based); 2) ad-hoc working group participants experts who attended specific working group meetings relevant to their expertise (23 total: 7 US-based, 5 Africa-based, 5 UK-based, 4 EU-based, 2 Australia-based); and 3) contributors who provided written or verbal comments for working group consideration (10 total: 4 US-based, 6 UK-based).

James et al. (2018) also prescribe engagement in risk assessment in a limited fashion. In describing the importance of aligning risk assessment protection goals to the relevant national context, James et al. (2018) state: "Thus, there will need to be a plan for how public input on hazards is solicited and integrated"(p. 8). Beyond highlighting the need for public input on hazard identification, there is no further discussion of who would be involved, how it would take place, the challenges involved with such an effort for gene drive technology, or how engagement should be involved in other parts of risk assessment. The authors do discuss engagement more broadly, saying for example "most of the African population legitimately falls in the category of stakeholder regardless of where the trials begin" and that "community engagement should not be conflated or mistaken for public relations or marketing and does not imply advocacy"(p. 9, 11). However, these statements place engagement within a sequence of events *after* the risk

assessment stage, not during, and generally speak of it within the context of gaining local community consent for field trials.

Both Roberts et al. (2017, D2) and Teem et al. (2019, D8) present findings from workshops conducted on the topic of problem formulation for gene drive technology to address malaria causing mosquitoes. While these efforts both represent examples of conducting engagement for risk assessment (given they seek to substantively inform problem formulation for future risk assessments on gene drive technology to address malaria causing mosquitoes), they are also risk assessment guidelines (given they present findings to influence *how* gene drive risk assessment is conducted going forward). Overall, they both provide only vague calls for engagement in risk assessment.

Roberts et al. (2017) publish the results from a FNIH convened US-based workshop titled *Problem formulation for the use of gene drive in mosquitoes.* This expert workshop explored the potential use of gene drive technology to address malaria-causing mosquitoes in sub-Saharan Africa, and focused on the problem formulation stage of risk assessment to identify pertinent protection goals. Participants were largely from the EU and US (Europe/US=34, Africa=8, Other=5). In prescribing engagement in risk assessment, Roberts et al. (2017) focus vaguely and narrowly on protection goals stating, "It is also important to consider that there may be different perspectives on environmental protection goals… The authors would encourage these considerations to be taken up in appropriate forums, and particularly in communities where the use of gene-drive technologies would likely occur" (p. 533).

Teem et al. (2019) summarized the findings from four regional consultations on the problem formulation step of gene drive risk assessment convened by the FNIH and the African Union's New Partnership for Africa's Development (NEPAD). These consultations occurred in Ghana (2016), Kenya (2017), Botswana (2017) and Gabon (2018). Participants in these consultations included stakeholders from African human health and environmental agencies, local and international scientists, and government officials. Participants in the consultations identified protection goals and pathways to harm that could result from the use of gene drive technology to

address malaria causing mosquitoes. The goal in identifying these protections goals and pathways to harm was to help inform future risk assessments on gene drive technology. In prescribing engagement in risk assessment, Teem et al. (2019) focus vaguely and narrowly on identifying topics or potential adverse effects to take up in a risk assessment, saying "Prior to the release of any such technology, it is important to hold conversations to help define the areas of concern that will likely need to be addressed in those risk assessments" (p. 11).

The vague and narrow prescription for engagement in risk assessment by both Roberts et al. (2017) and Teem et al. (2019) is noteworthy given these documents are themselves the result of engagement in risk assessment and are clearly addressing the issue of problem formulation. Problem formulation in risk assessment clearly involves a host of important judgments beyond identifying protection goals and potential adverse effects, including for example: identifying risk pathways, deciding what additional evidence is required, and deciding on an analysis plan. This absence of a broader envisioning for engagement in risk assessment is consequential, as we discuss in Section 4.

Finally, in 2019, the Secretariat of the Convention on Biological Diversity (CBD) published a draft report entitled *Study on risk assessment application of annex I of decision CP 9/13 to living modified organisms containing engineered gene drives* (Smets & Rudelsheim, 2019, D9). The report was to stimulate discussion on an online forum and provide input to the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management – both addressing risk assessment issues relating to gene drive technology. The report draws on documentary analysis, stakeholder meetings, expert-stakeholder interviews, and a review of existing risk assessment processes. While Smets and Rüdelsheim (2019) explicitly mention engagement in risk assessment, they do so only in passing during a discussion of the challenges of facing gene drive risk assessment. Their prescription of engagement for risk assessment consists solely of the statement: "technical and methodological challenges will likely render the risk assessment for engineered gene drive applications more detailed and more complex, also requiring public consultation"(p. 6). This point is undeveloped, leaving unsaid exactly what such public consultation could lead to addressing technical and methodological challenges, how they would need to be structured, who

should be involved, and the challenges facing such an effort. This vague call for public consultation around risk assessment leads to more questions than answers and falls short compared to the next examples that incorporate a substantive discussion of engagement for gene drive risk assessment.

3.3. Guidelines that substantively prescribe engagement in risk assessment

Three documents from the data set (D5, D7, D10) offered a more detailed, substantive discussion of engagement in gene drive risk assessment (Table 3).

Table 3. Illustrative quotes demonstrating the prescription of engagement in risk assessment that included substantive discussion of engagement in gene drive risk assessment

D5: *Identifying and detecting potentially adverse ecological outcomes associated with the release of gene-drive modified organisms* (Hayes et al., 2018) **"Hazard analysis techniques… are good ways to include a diverse set of interested and affected parties in hazard identification, including those with practical experience with relevant environmental systems. Here we emphasize the need for active participation of interested and affected parties throughout the analysis process, rather than simply communicating the results of the process to these parties. Efficacious stakeholder participation in the phased testing and release process will require a scientifically literate, neutral, and seasoned facilitator (Kaner et al. 2007)." (p. 13) "If a decision is taken to move forward with the GDMO, then the process of identifying potential risks of the GDMO, risk management strategies for potential containment failures and acceptance of criteria for progression through each phase of the testing and release pathway should continue to involve relevant stakeholders (Dana et al. 2014)." (p. 14)**
D7: *Towards inclusive social appraisal: risk, participation and democracy in governance of synthetic biology* (Stirling et al., 2018) **"Since the answers obtained in risk assessment depend on both questions and assumptions, the point becomes clear that if risk assessment itself is to be regarded as rigorous, then it needs to be as systematic and robust about its own qualitative framing conditions as it already tries to be about quantitative data and analysis [28]. So, public participation should not be seen as a matter of 'political correctness' or as a means to achieve a pre-conceived end, but rather as inherent to the rigour and effectiveness of regulatory assessment."(p.44)** **"It is widely recognised to be essential, at least for novel technologies such as gene drives, that 'the public' are engaged in the opening steps of the first (identify, define and agree) stage of a risk assessment process." (p.45)** **"Stakeholders can at this point make useful contributions to: (i) defining the boundaries and scope of the assessment, for instance concerning which alternatives are considered; (ii) describing conceptual models of the environmental and socio-economic systems that the options will interact with; (iii) identifying valued components or processes of these systems (assets); and (iv) identifying circumstances that could lead to adverse outcomes (hazards) if the technology is deployed. Facilitated discussions with broad groups of stakeholders at this stage have been shown to improve the conceptual understanding of systems and the hazard identification stage [34]."(p.45-46)** **"It is still possible, but somewhat more difficult, to engage publics around the formulation of what in risk assessment parlance are termed 'loss functions'… It is also essential for interested and affected communities to be engaged in this second stage of the risk assessment procedure around issues of "acceptability"."(p. 46)** **"Potential obstacles to public participation in the crucial first steps of the first stage of a risk assessment include language barriers, conflicting styles of knowledge, and availability and accessibility of information."(p.48)**

D10: ***Evaluation of existing EFSA guidelines for their adequacy for the molecular characterization and ERA of genetically modified insects with synthetically engineered gene drives*** **(EFSA, 2020)**
"Enhanced dialogue between risk assessors, risk managers and stakeholders is advocated to define clear protection goals and decision-making criteria for the ERA of GDMIs." (p. 1)
"In addition, active stakeholder engagement on problem formulation (including the setting of protection goals and assessment endpoints) can improve the value of ERA, as it may help to ensure that ERA are meaningful and informative to the environmental decisions that affects them (e.g. Nelson et al., 2009; NASEM, 2016; Kuzma, 2019; Burgess et al., 2019). In the context of the potential deployment of a gene drive as part of a malaria eradication strategy, researchers, donor organisations and stakeholders, ethicists, health professionals, government regulators in the fields of environment health and biosafety as well as government policymakers have embarked on a series of consultations, workshops and public engagements aimed at problem formulation for the use of gene drive modified mosquitoes to reduce malaria incidence (e.g. Roberts et al., 2017; James et al., 2018; Teem et al., 2019). These types of consultation provide a helpful format to identify relevant protection goals (Craig et al., 2017; Hokanson et al., 2018) and frame ERA (Murphy et al., 2010; Kolopack et al., 2015; Murray et al., 2016). If risk managers consider such an engagement useful to define protection goals, they may want to explore how it should be best designed, and whether it should be performed on single applications, groups of applications, or on the technology per se." (p. 39)
"Enhanced dialogue between risk assessors and risk managers along with stakeholder/societal engagement is required to define protection goals, decision-making criteria and the identification of pathways to harm for the ERA of GDMIs." (p. 62)

Hayes et al. (2018, D5) examine how to identify hazards and potential adverse effects as part of gene drive risk assessment. The article emerged from a 2016 workshop convened by the Genetic Engineering and Society Center at North Carolina State University called "A roadmap to gene drives: A deliberative workshop to develop frameworks for research and governance." The interdisciplinary workshop explicitly addressed risk assessment and resulted in a special issue published in the *Journal of Responsible Innovation* and of the articles, only Hayes et al. had a detailed enough discussion of risk assessment to be classified as guidelines. The individuals who were involved with Hayes et al. included 10 people from the Australian research organization CSIRO, one US-based expert in risk assessment and engagement, and one Australian-based expert in risk assessment. Hayes et al (2018) make three noteworthy choices in their prescription of engagement for risk assessment: 1) they specify *what* they mean by engagement and *who* should be involved; 2) they specify *when* in risk assessment engagement should take place, and 3) they discuss specific aspects of *how* engagement should be conducted. First, Hayes et al. (2018) define the engagement they prescribe in opposition to engagement efforts that seek to communicate results to stakeholders. Instead, they specifically call for "active participation of

interested and affected parties" (p. 13). Second, they argue that engagement should take place during the hazard identification process as well as in discussing acceptance criteria. Third, they discuss specific aspects implementing engagement by calling for "a scientifically literate, neutral, and seasoned facilitator" (p. 13). The explicit mention of these points is a limited but important progression compared to the documents discussed in Section 3.2.

Stirling et al. (2018, D7) emerged from a second workshop held at NCSU on gene drive governance, titled "Environmental release of engineered pests: building an international governance framework." This interdisciplinary expert workshop was convened with the Australian Government agency, Commonwealth Scientific and Industrial Research Organization (CSIRO) and funded by the OECD. The workshop produced a 2018 special issue in the journal *BMC Proceedings*. Stirling et al. (2018) explore in detail why, where, and how engagement should take place in risk assessment for gene drive technology and other synthetic biology applications. The authors from Stirling et al. included an expert in ecological risk assessment based in Australia, an expert in engagement base in the US, and an expert in engagement in risk assessment based in the UK.

Stirling et al. (2018) begin by reviewing, in detail, the arguments for why it is important to include engagement in risk assessment. Next, they offer a detailed diagram of a risk assessment process for gene drive technology and highlight steps that are: 1) essential for engagement and easily facilitated; 2) essential for engagement but harder to achieve; 3) essential for engagement but difficult to achieve; and 4) potentially useful but not essential. They then provide a discussion of key risk assessment steps and how, why, and with whom to conduct engagement. For example, they describe why engagement needs to be involved in problem identification, the selection of assessment endpoint, and the definition of risk acceptance criteria. They also discuss key challenges facing engagement such as: cost, conflicting styles of knowledge, potential conflict of interests, the fast pace of development, and the complex nature of gene drive technology. They conclude by discussing some practical methods that can be used to achieve engagement in risk assessment. Stirling et al. epitomizes what it looks like to move beyond a vague call for engagement in risk assessment towards a detailed, substantive, and careful

consideration of the issues involved in doing so. Overall, this prescription of engagement in risk assessment is the broadest and most in-depth of any we have found.

In January 2020, EFSA's GMO Panel published its Draft Scientific Opinion, *Adequacy of existing EFSA guidelines for the risk assessment of gene drive modified insects* (Naegeli et al., 2020, D10). This document was commissioned by the European Commission and authored by a 5 person (3 UK-based, 1 France-based, 1 Germany-based) working group. In addition to meeting 22 times, the working group conducted a stakeholder workshop and invited 7 ad hoc experts to contribute to specific working group meetings. The Draft Scientific Opinion explored whether gene drive technology could pose novel hazards and whether and how to update existing risk assessment guidelines for genetically modified animals to address gene drive technology.

Naegeli et al. (2020) make a variety of noteworthy choices in prescribing engagement in risk assessment: 1) they specify where in risk assessment engagement should take place, 2) they cite existing literature on engagement in risk assessment, and 3) they call attention to the need for further consideration of how engagement should be conducted. First, they advocates for the use of stakeholder engagement in problem formulation, specifically to help define "protection goals and decision-making criteria" and identify "assessment endpoints" and "pathways to harm" (p.1, 39, 62). Second, they cite some of the existing prescriptive literature on engagement in risk assessment (e.g., Nelson et al., 2009) as well as existing examples of engagement on problem formulation related to gene drive modified mosquitoes (Roberts et al., 2017; EFSA, 2020: 39). While they notably do not cite Stirling et al. (2018), the fact that they do cite some previous literature makes explicit that there is scholarship to build from in designing engagement and that these ideas are not new. Third, while omitting discussion on how such engagement should be structured, they highlight the need for such work arguing, "If risk managers consider such an engagement useful to define protection goals, they may want to explore how it should be best designed, and whether it should be performed on single applications, groups of applications, or on the technology per se" (EFSA, 2020: 39).

4. The challenges facing engagement in risk assessment

ERA will be a significant component of governance decisions about whether and under what conditions to use gene drive technology. Currently, regulators, policy-makers and international actors are evaluating the adequacy of existing regulators and ERA guidelines for gene drive governance. ERA guidelines will influence what form future ERAs for gene drive technology will take, including what role there is for engagement. We identified ten key documents that emerged from an interdisciplinary workshop or working group and have contributed to this process by prescribing ERA for gene drive. We examined these documents to explore whether and how they prescribe engagement in ERA for gene drive technology.

Our findings show a significant gap in how engagement in ERA for gene drive technology is being prescribed. First, some guidance documents do not prescribe a role for engagement in gene drive ERA at all (D1, D4). Second, some guidance documents prescribe a role for engagement but only in vague or very narrow way (D2, D3, D6, D8, D9). Finally, of the three documents that begin to substantively prescribe engagement in ERA (D5, D7, D10), only one document (D7) prescribes engagement in a substantively thorough and detailed way. Across all of these documents – with one exception – we see an overall vague and narrow prescription of engagement in gene drive ERA. Furthermore, we found that a small set of organizations are convening the influential events leading to these gene drive ERA guideline documents (see Table 1). While the small set of organizations convening these events should be lauded for beginning conversation on this important topic, there should also be concern about such a small number of organizations solely influencing these conversations. More organizations from a broader set of countries, including those outside the Unites States and Europe, should be involved with efforts on ERA guidelines so that the events reflect a variety of cultural contexts and perspectives. This is especially important given that one of the first potential uses for gene drive technology is likely to be in Africa for malaria-causing mosquitoes.

One consequence of vague prescriptions of engagement in risk assessment is that it is unclear what exactly is being called for. If not specified, engagement may end up taking the form that is

easiest, cheapest, or least threatening to the status quo. Engagement can mean many things and, in addition, a broadly agreed upon norm for what form engagement in risk assessment should take does not exist. Hartley and Kokotovich (2018), for example, discuss how engagement can be incorporated into all steps of risk assessment, with who is involved and how engagement is structured varying across steps. At the same time, many include not only two-way participation but communication and consultation beneath the umbrella of 'engagement' (Rowe & Frewer, 2005). It is unclear within vague calls for engagement whether actors are calling for education or the substantive involvement of stakeholders. This becomes particularly problematic when there are powerful actors who may influence status quo decision-making. Vague ideas of engagement allow superficial, non-substantive practices to stand in for rigorous and impactful engagement. For a technology where indigenous and community perspectives are frequently discussed as important (e.g., Convention on Biological Diversity, 2018), this type of vagueness may problematically thwart the full potential of engagement. Engagement is difficult and costly, so without clear guidance it is unlikely to occur at all and if it does, it will take the path of least resistance, in the form of more traditional risk communication which falls short of the potential for engagement.

Even within the three documents that substantively prescribed engagement in gene drive risk assessment (D5, D7, and D10), two of them (D5 and D10) remain crucially limited. First, although these two documents highlight the importance of engagement within the components of problem formulation (e.g., identifying protection goals, assessment endpoints, or pathways to harm) they do not discuss the potential role of engagement within the other steps of risk assessment (e.g., exposure and effects analysis, risk characterization). A rigorous envisioning of engagement for risk assessment should consider its potential within all steps of risk assessment (Hartley & Kokotovich, 2018). The impetus for engagement in problem formulation is also relevant within the rest of risk assessment – namely the existence of value judgments or decisions that actors would make differently based on their expertise or worldview. While the type of value judgment is different within the analysis or risk characterization step and may

require a certain amount of expertise, their role for contextually-designed engagement to help inform them remains (Kokotovich et al. 2020).

While documents D5 and D10 pay some attention to issues of process, there is inadequate exploration of the challenges that impede efforts to pursue engagement in risk assessment. These include challenges facing many engagement efforts around science and technology, such as: Who are the relevant stakeholders? What type of expertise is needed to substantively engage in the different steps of risk assessment? How should conflict be dealt with? How to ensure that marginalized views (politically or epistemically) are included within engagement? Furthermore, engagement challenges specific to gene drive technology exist which these documents do not substantively discuss, for example: How do you identify relevant stakeholders for a technology that may be designed to spread? If certain stakeholders view a gene drive technology-induced extirpation of a particular species as something that would reverberate through an ecosystem in previously unexperienced ways, how do you decide which of a potentially endless list of assessment endpoints and pathways to harm to focus on? Without acknowledging these challenges, assessors may assume engagement is a straightforward and easily accomplished action, when in reality it is a challenging topic in need of rigorous attention.

Without question, the document with the most substantive and detailed discussion of engagement in risk assessment was Stirling et al. (2018). Two of the factors that may have contributed to this are: 1) the article emerged from an interdisciplinary workshop contributing to the building of a "participatory, proactive" gene drive governance framework (NCSU/GES & OECD, 2016) and 2) the authors of the article include an expert in environmental risk assessment, an expert in engagement, and an expert in engagement and the politics of risk. While a single article cannot explore the breadth of issues surrounding engagement in risk assessment, Stirling et al. do a noteworthy job of laying out a variety of key issues for consideration. Surprisingly, this article is not cited in any of the other documents we examined coming after it, including the major CBD and EFSA reports. Future study could take up the important questions of how to further this work and why this article was not cited in these subsequent reports.

Overall, then, our findings reveal the limited nature of how engagement in ERA for gene drive technology is being prescribed. These limitations may seem surprising given that there has long been both a recognition of the values-laden nature of risk assessment (e.g., see discussion of "Risk Assessment Policy" in National Research Council, 1983) and calls for engagement in risk assessment (Fischer, 1991; Stirling, 1998). There are, however, a host of challenges facing engagement in ERA that may contribute to these limitations. First, there continues to be an undue focus on rationalizing engagement in ERA. This may exist due to lingering "deficit model" views (McNeil, 2013), concerns about challenges facing engagement (Webler & Tuler, 2018), or deeply ingrained but mistaken views about the purely scientific or value-neutral nature of risk assessment (Elliott, 2019). Constantly rehashing the questioning of whether engagement in ERA is needed prevents necessary discussions and scholarship concerning *how* to conduct engagement in risk assessment. At the same time, rationale is one important consideration when designing and conducting engagement, since some may use engagement to pursue communication while others may pursue it to substantive two-way deliberation. But even these discussions about rationale need to move away from *whether* to conduct engagement (e.g., yes/no) to questions of *why* and *how* (e.g., To achieve what? To include who? Using what methods?).

A second challenge facing engagement in ERA is the conflation of engagement in ERA with engagement in risk governance or risk analysis. Risk assessment is only one important component of risk governance (or risk analysis). When engagement in risk governance is called for, it is often not clear whether that is referring to engagement in risk management, engagement in risk assessment, or both. Without specifying a role for engagement in risk assessment, calls for engagement in risk governance tend to land in the risk management realm where the role of values in decisions is more acknowledged and comfortably navigated. Furthermore, calls for engagement to help bring ethical, justice, or socio-economic considerations into the risk governance process can unwittingly be seen as addressing all engagement needs within risk governance including with regards to risk assessment. While there is a need to consider ethics, justice, and socio-economic considerations in decision making that is informed by a risk

assessment, if engagement is not part of the risk assessment itself, the very goals associated with ethics and justice may be at risk. In other words, if engagement in risk assessment does not take place, then any resulting discussion about how to make ethical or just decisions based on the risk assessment is inherently flawed since the risk assessment itself is lacking.

To address this problematic status quo concerning the prescription of engagement in ERA for gene drive technology, we believe that there is a need for further empirical and theoretical attention to engagement in ERA for both guidelines and individual case-by-case ERAs. The existing literature on engagement in ERA represents a starting point, but the dearth of scholarship grappling with *how* to conduct engagement in ERA and the lack of these ideas being taken up in areas such as gene drive makes it clear that much more work is needed. In other words, while it is certainly good to see that efforts are being made to conduct workshops on engagement related to gene drive governance (Teem et al., 2019; Delborne et al. 2018), there is a need to deepen the focus on risk assessment itself and broaden who is involved. One way this can be furthered is through interdisciplinary teams who can bring their disciplinary strengths to bear on this thorny problem. One insight from the strength of the Stirling et al. (2018) article is that it would be beneficial for interdisciplinary teams to include scholars who have expertise in engagement and ideally engagement in risk assessment. It is hard to expect experts who have no experience or expertise in engagement to design engagement in risk assessment – targeting the right type of expertise to help further this work is essential.

Risk governance is a critical stage in the development and testing of emerging biotechnologies. The legitimacy of risk governance decisions rely on ERA. Engagement in ERA provides not only democratic legitimacy by involving those with a ‘stake’ or ‘interest’ in the issue, but substantive rigor into risk decisions by including actors who have knowledge to contribute to the robustness and scientific legitimacy of ERA. Such engagement is unlikely to occur if it is not specified clearly and substantively in ERA guidelines. The fact that this is not taking place is concerning for the future of gene drive technology and highlights a significant theoretical and empirical gap in the ERA literature.

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