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Engagement on risk assessment for gene drive mosquitoes by EFSA and Target Malaria

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ABSTRACT

As engineered gene drive technologies continue to advance, many actors are actively considering how environmental risk assessments (RAs) for gene drive organisms should be conducted, and how stakeholder engagement opportunities should be provided. There is, however, a lack of clarity concerning what constitutes engagement on gene drive RA and, furthermore, what forms of engagement already exist around gene drive RA. To address this gap, we reflect on the actions of a risk assessor (the European Food Safety Authority, EFSA) and a gene drive developer (Target Malaria) to understand: 1) the RA-related decisions that each are making concerning gene drive technology for mosquitoes and other harmful insects, 2) the existing role of engagement in those decisions, and 3) the implications for our understandings of engagement and RA. We found, first, that both EFSA and Target Malaria have already made many RA-related decisions, even though any preparation and evaluation of a formal RA for gene drive mosquitoes remains far off. This finding supports the idea that gene drive RA involves multiple processes and decisions in different forms across the entire technology and regulatory development process. Second, we found that both EFSA and Target Malaria have already integrated engagement into their respective RA-related decisions in different ways, reflecting their different roles. We conclude by considering how EFSA and Target Malaria could improve their existing RA-related engagement by explicitly considering disciplinary diversity *and* worldview diversity in their related decision making.

1. Introduction

Scientists are combining gene-editing techniques and synthetic biology to engineer gene drives in sexually reproducing animals. Individuals carrying an engineered gene drive (which biases its own inheritance) can pass specific genetic changes to their offspring, enabling a genetic change to increase in frequency and spread through interbreeding target populations. Depending on the engineered gene drive system, theoretically, a genetic change of interest could spread through target populations and persist indefinitely, or could be restricted in its spread or persistence. Scientists are currently exploring the use of engineered gene drive technologies in areas of global health, conservation and agriculture. The most advanced cases involve the use of engineered gene drives to suppress or replace target populations of disease vectors such as mosquitoes that cause malaria. To prepare for potential environmental releases (i.e., field trials) of gene drive organisms, developers, policy-makers, regulators, risk assessors, engagement practitioners and academics are considering how to conduct environmental risk assessment (RA) for such organisms (Connolly et al., 2021; Devos et al., 2021a, 2021b, 2020a; Long et al., 2020).

Numerous calls for engagement relevant to RA have been integrated into these efforts (Connolly et al., 2022; Delborne et al., 2018; Devos et al., 2021a; NASEM, 2016; WHO, 2021). NASEM (2016: 131) defines engagement in the context of gene drive as "seeking and facilitating the sharing and exchange of knowledge, perspectives, and preferences between or among groups who often have differences in expertise, power, and values". Three justifications are often provided for such engagement, including that it leads to more effective decisions, it leads to trusted decisions, and people have a democratic right to inform decisions that affect them (NASEM, 2016; Stirling, 2008). Engagement in the context of RA means inclusive processes to incorporate values, knowledge and experience external to the developers and risk assessors

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(e.g. Connolly et al., 2022; Hartley et al., 2022). Engagement in RA is an important component of the broader conversation about who gets to decide whether and how biotechnologies should be used (Hartley, 2016; Stirling et al., 2018; Wickson and Wynne, 2012). Some scholars have explored how engagement could be incorporated into gene drive RA (Kokotovich et al., 2020; Kuzma, 2019; Stirling et al., 2018). However, there remains a lack of empirical cases examining engagement designed to inform gene drive RA processes (Kokotovich et al., 2022). Further, a recent analysis of documents contributing to the development of guidelines for gene drive RA, which lay out how to conduct RAs and what should be included in them, reveals a significant gap in how engagement should be incorporated, particularly a lack of detail about how to conduct engagement relevant to RA (Hartley et al., 2022).

To augment the literature exploring the current and potential role for engagement in gene drive RA, we explore two distinct case studies involving gene drive mosquitoes – one involving a risk assessor and one involving a gene drive developer. Our objective is to better understand the RA-related decisions that each are making, the existing role of engagement in those decisions, and the implications for future understandings of engagement relevant to RA. The risk assessor is from the European Food Safety Authority (EFSA) which reports to the European Commission and has been actively involved in the development of RA guidelines for environmental releases of gene drive organisms, including mosquitoes. The gene drive developer is one of the teams in the Target Malaria research consortium, working to develop gene drive mosquitoes with national partner institutes that are likely to be among the first to apply for the environmental release of a gene drive organism. Both actors play important, yet different roles related to gene drive RA and both have initiated engagement related to RA.

EFSA has conducted engagement to inform its analysis of the adequacy and sufficiency of existing RA guidelines for assessing the risks from gene drive insects, including mosquitoes. Typically, it collects and analyses existing research and data and provides scientific advice to support decision-making by risk managers, which includes the development of guidelines for developers to follow as they prepare applications that require RA. At the point where an application would be made in Europe, EFSA would respond to a request from a risk manager for a RA opinion. EFSA also has a clear mandate to conduct engagement. One of EFSA's five key values is "openness", which it describes in the following way: "Communicating openly and promptly on its scientific work helps foster trust in EFSA. As well as being transparent, we aim to engage civil society in our risk assessment work and connect with untapped scientific potential" (EFSA, 2022). EFSA, because of its scope as a risk assessor and its public mandate, addresses a more delineated set of RA-related questions compared to the broader development-oriented scope of Target Malaria, in which product specifications are continually focused until a final product-specific application is achieved. For Target Malaria, the gene drive product development process has involved a range of choices related to how it identifies information needs, generates relevant evidence and makes decisions affecting a potential product RA. Target Malaria also has a commitment to engage and co-development is one its four core values, which is heavily focused on engagement (Roberts and Thizy, 2022).

Despite the related activities of technology developers and risk assessors in developing processes for RA, few articles examine their activities and decisions at the same time. Much of the empirical literature on RA is focused on risk assessors' activities, while the background decisions made by product developers leading up to a formal product RA have been less well documented until recently (e.g. Connolly et al., 2021). As a collaboration of a risk assessor, a developer academic and social science academics, we describe and reflect on: 1) EFSA's decisions involved in the evaluation of the adequacy and sufficiency of existing RA guidelines for gene drive technology for harmful insects, including mosquitoes; 2) Target Malaria's decisions involved in the development of gene drive mosquitoes for malaria control that may inform formal RAs for product tests; and 3) how engagement is conducted across both of these processes. Our broad goal is to both clarify and improve how engagement related to RA is conducted for gene drive mosquitoes. Importantly, while we are examining the existing forms of engagement related to gene drive mosquito RA, we are not analyzing the findings from these engagement activities. Such an analysis would require its own study. Rather, we are focusing solely on understanding the existing decisions being made by EFSA and Target Malaria related to gene drive mosquito RA and what form engagement is taking within these decision-making processes.

Our findings are noteworthy for multiple reasons. First, we describe how EFSA and Target Malaria have made many diverse RA-related decisions prior to any formal RA. This supports the notion that RA-related decisions involve more than just the formal process associated with a technology developer's preparation of a dossier and a risk assessor's application review. They also include a series of initial decisions made during the technology development and regulatory assessment processes by both developers and risk assessors/regulators, respectively. This finding brings greater transparency and clarity to these initial RA-related decisions and their importance. Second, EFSA and Target Malaria have already conducted different types of engagement to inform these RA-related decisions. In describing the two cases, we contribute to the scholarship on engagement in RA and help to improve processes related to RA for gene drive organisms and other genetically modified organisms. Finally, we propose that engagement for RA-related decisions should be for both epistemic and democratic ends. For epistemic engagement, this requires strengthening the traditional focus on disciplinary diversity, but also broadening the engagement to include worldview diversity.

2. Methods

We chose to employ case studies of gene drive technologies for our methodology because such technologies contribute key insights about RA and engagement (Flyvbjerg, 2006). First, it is likely that one of the Target Malaria partner institutes in Africa will spearhead the first environmental release of an engineered gene drive organism, although there is no expectation that Target Malaria would make applications in Europe or that EFSA would have any formal role in support of regulatory decisions outside of Europe. Second, the openness of the actors involved in gene drive (Ledingham and Hartley, 2021) brings the opportunity for additional insights about what form RA will take and potential roles for engagement. Third, the insights gained from this study have implications not just for gene drive technologies, but also for other instances of RA, especially in other cases of RA where engagement is desirable.

The collaboration was dependent upon bringing together different co-authors' expertise and experience in order to provide new insights on the topic addressed. The co-authors include: 1) a professor at the University of Exeter with expertise in politics, science and technology studies (STS), risk analysis, and the governance of genetically modified organisms (GMOs) and gene drive technologies; 2) a postdoctoral research fellow at the University of Exeter with expertise in STS, engagement, risk analysis, and emerging technology governance; 3) a senior scientific officer at EFSA with expertise in biological/ecological sciences and experience in environmental RA and the development of RA guidelines for GMOs including gene drive insects; and 4) a professor at Imperial College London with expertise in invasive species management, agricultural economics and risk analysis who is leading Target Malaria's risk analysis for gene drive mosquitoes. This collaboration allows a critical reflection on processes in which each of the participants played a part, and presents an opportunity to learn from different perspectives (as done in other arenas, e.g., Zwart and Nelis, 2009).

This collaboration drew upon key insights from a variety of literature, including multi-sector collaboration (Rod and Paliwoda, 2003), collaborative evaluation (Rodríguez-Campos, 2012), and responsible innovation (Steen, 2021). The collaborative process involved the following steps. First, the impetus for the collaboration involved an

intersection of common interest and diverse expertise on the same topic. This shared interest was identified when all four authors presented their work at an interdisciplinary workshop on synthetic gene drives ("Interdisciplinary Workshop on Synthetic Gene Drives, ", 2021). Second, the group met to identify the overarching questions of the collaboration, followed by individual meetings. One line of questions explored EFSA's process and related decisions involved in the evaluation of the adequacy and sufficiency of existing RA guidelines for gene drive technologies for harmful insects including mosquitoes. Other conversations explored the process and related decisions involved in the development of gene drive mosquitoes for malaria control by Target Malaria, leading to applications requiring a formal RA. The discussions focused on how engagement was conducted in these processes. The decision processes and related engagement were mapped, and then all four authors met to discuss the initial findings and their implications. A draft manuscript was reviewed and further discussed by all authors through meetings and email exchanges. Target Malaria has a standard publication quality review process for authors who are part of the project and changes were made to the manuscript to address reviewer comments.

3. Two case studies of engagement on risk assessment

3.1. EFSA and risk assessment guidelines for gene drive insects

EFSA's function is to advise on the safety of the food chain in Europe from farm to fork. With its food safety assessments, EFSA – together with European Union (EU) Member States – contributes to the protection of human, animal, plant and environmental health and animal welfare. Within its purview of food safety, the environmental release of GMOs, including gene drive mosquitoes, is subject to RA and regulatory approval. In the risk analysis process, the role of risk assessors such as EFSA is to assess any plausible risk that a proposed environmental release of a GMO may pose to human and animal health and the environment, and recommend options for risk mitigation, if necessary, to risk managers. Decisions to approve a release, given potential risk management, are taken by risk managers. EFSA's scientific advice on the RA of GMOs is given through its scientific Panel on GMOs, which consists of scientific experts from EU research institutes, universities or RA bodies. Besides the assessment of environmental releases of GMOs, EFSA is responsible for the development of RA guidelines.

To date, EFSA's key contribution to gene drive RA has been the development and publication of a Scientific Opinion which evaluates the adequacy of its existing RA guidelines for gene drive (EFSA GMO Panel, 2020). While gene drive technologies have been mentioned in EFSA's previous genetically modified (GM) animal RA guidance (EFSA GMO Panel, 2013), the first formal attention to gene drive RA, which led to this Scientific Opinion, came as a result of an EC mandate to EFSA in 2018. International discussions on gene drive governance were to take place at the Cartagena Protocol on Biosafety Meetings of the Parties in 2020 (Keiper and Atanassova, 2020). To prepare, the EC asked EFSA to assess whether its existing RA guidance for GM animals (EFSA GMO Panel, 2013) is adequate (i.e., of a minimum quality threshold, but requiring additional guidance) and sufficient (i.e., fit for purpose as is without need for further guidance) for gene drive technologies and what the possible risks from such technologies might be. While the EC often mandates EFSA to develop new guidelines for a particular technology proposed for use, given that gene drive technologies are still under development and not yet being proposed for use in the EU, the EC decided to first focus on the adequacy and sufficiency of existing RA guidelines. The EC mandate requested that EFSA:

"assess, through a problem formulation exercise, whether: (1) the deliberate release of genetically modified organisms (GMOs) containing engineered gene drives (termed hereafter as gene drive modified organisms [GDMOs]) could pose risks and potential novel hazards to human/animal health and the environment, considering relevant comparators; (2) the scientific considerations/requirements given in its previously published guidelines for the risk assessment of genetically modified animals (GMAs) (EFSA, 2013) are adequate and sufficient for GDMOs; and (3) there is a need for updated guidance in relation to previous documents (EFSA, 2013)." (EFSA GMO Panel, 2020, p. 3).

One of EFSA's first tasks was to negotiate the mandate. As a result of the standard negotiation process between EFSA and the EC, the scope of the mandate was, at EFSA's request, narrowed to focus on gene drive technology related to harmful insects (e.g., disease vectors, agricultural pests and invasive species) and broadened to include a stakeholder workshop and online consultation (EFSA GMO Panel, 2020, p. 10). EFSA worked with its GMO Panel to begin the process of developing the Scientific Opinion. The GMO Panel is a standing committee currently composed of 16 scientists who come from EU research institutes, universities or RA bodies, and have expertise in food and feed safety, environmental RA, and molecular, phenotypic and compositional characterization of GM plants and derived food and feed products. The GMO Panel, with the support of its expert working groups and EFSA, provides scientific advice to risk managers such as the EC and European Parliament on any possible risks that the deployment of GMOs may pose to humans, animals and the environment (EFSA, 2021). To fulfill its mandate, EFSA and the GMO Panel designed and implemented four formal processes, outlined in Fig. 1, that included: 1) creation of an expert working group and selection of its chair (EFSA and the Panel's responsibility); 2) stakeholder workshop (EFSA's responsibility); 3) hearing expert testimony to the expert working group (EFSA and chair of expert working group's responsibility); and 4) online public consultation (EFSA's responsibility). These four processes contributed to the development of the Scientific Opinion on the adequacy and sufficiency of existing RA guidelines for gene drive insects. YD was the EFSA project manager for the Scientific Opinion and JM contributed to the expert working group. The GMO Panel endorsed the resulting Scientific Opinion on October 14th, 2020 and it was published on November 12th, 2020.

Following the mandate negotiation, EFSA created the Gene Drive Expert Working Group ('expert working group'). The final expert working group consisted of five members (two from the GMO Panel and three external members) and met 22 times from February 7, 2019 to September 28, 2020 (EFSA GMO Panel, 2020). The selection of individuals for the expert working group was shaped by the need for: 1) entomological expertise to complement the GMO Panel's expertise, which is largely plant-related, and expertise with existing RA guidance development; and, 2) avoidance of potential conflicts of interest, as defined by EFSA policies (EFSA, 2018). In addition, selection was shaped by an implicit need for: 3) geographical representation and gender diversity; and 4) individuals who could work productively with others. The five members of the expert working group were men from the United Kingdom (3), France (1), and Germany (1) with expertise in arthropod genetics, insect biotechnology, disease vector/pest control strategies, ecological modelling, community ecology, the molecular characterization of GMOs, environmental RA of GM insects, and RA of invasive species (EFSA GMO Panel, 2020). The GMO Panel tasked them to assess whether the existing EFSA RA guidance for GM animals was adequate and sufficient for the molecular characterization, environmental RA, and post-market environmental monitoring of gene drive insects (EFSA GMO Panel, 2020, p. 12).

The third set of decisions involved a stakeholder workshop, which was an unusual and noteworthy engagement activity for EFSA. This was the first time that EFSA had, in the field of biotechnology, held such a workshop early in the process. EFSA believed such an engagement activity was necessary due to the nature of the current social debate on gene drive technologies (e.g., Foote, 2020), the need for greater dialogue, and the need to align with its policy on openness and transparency (EFSA GMO Panel, 2020). The workshop was held on 15th May, 2019, relatively early in the expert working group's process (Feb-Sep), with the goal to invite stakeholders to discuss the potential risks

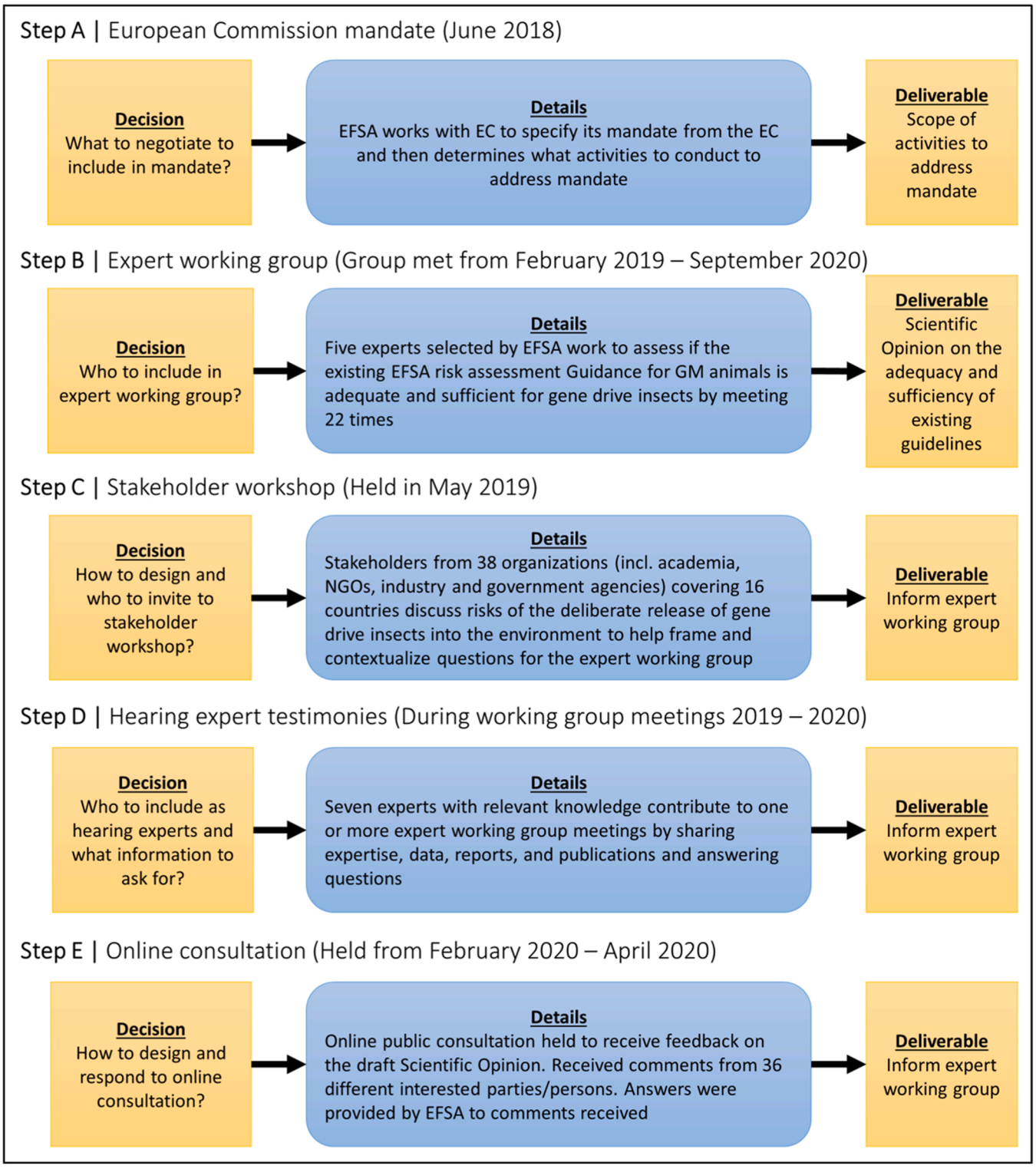

Fig. 1. Key steps in EFSA's pathway for evaluating the adequacy of existing RA guidelines for gene drive insects.

associated with the environmental release of gene drive insects to help frame and contextualize questions for the expert working group (Devos et al., 2020c). Stakeholder workshop participants were from 16 countries, represented 38 different organizations, and represented a variety of sectors including: academia, the non-governmental organization (NGO) sector, industry, and government agencies.

In the workshop, participants heard presentations from experts in the morning and in the afternoon discussed one of two hypothetical problem formulation exercises on low threshold gene drives (which are predicted to spread from a small number of released individuals) to control: 1) the Asian tiger mosquito (*Aedes albopictus*), a vector responsible for dengue transmission in southern Europe, and 2) Spotted-wing drosophila (*Drosophila suzukii*), a pest of soft fruits across much of Europe. EFSA sent briefing notes to workshop registrants ahead of the workshop, so they could prepare themselves. For each case study, stakeholders were invited to:

"(1) identify relevant broad protection goals and make them operational for use in environmental risk assessment;.

(2) formally devise examples of plausible pathways to harm that describe how the deployment of gene drive modified insects could be harmful;.

(3) formulate example risk hypotheses about the likelihood and severity of such events;.

(4) identify possible information that would be useful to test these risk hypotheses; and.

(5) identify how to acquire new data for hypothesis testing when existing information is deemed insufficient for regulatory decision-making." (Devos et al., 2020c, p. 1).

Results were captured in a summary report (Devos et al., 2020c) and the expert working group considered the outcomes of the stakeholder workshop in its formation of the Scientific Opinion. This workshop provided EFSA with valuable lessons for future stakeholder engagement activities. For example, discussion might have been more substantive if the workshop had been longer and included fewer participants to enable a more open dialogue on the full range of issues at stake. A professional moderator could have helped to facilitate discussions in the breakout sessions and avoided domination of the discussion by a few stakeholders, which hampered open and free deliberation. The issues under discussion were highly complex and to some extent novel, and the very technical and scientific framings of the subject matter limited the possibility to discuss the different worldviews underlying technical decisions of risk, which mattered for many stakeholders.

In the fourth step, EFSA and the expert working group chair jointly decided to invite seven other hearing experts with relevant knowledge to contribute to one or more expert working group meetings by sharing expertise, data, reports, and publications and answering questions. These expert scientists held the following types of expertise: arthropod genetics, conservation biology, insect biotechnology, disease vector/pest control strategies, ecology, molecular characterization of GMOs, environmental RA and post-market environmental monitoring of GM insets and RA of invasive species.

The last activity involved EFSA's online public consultation to receive feedback on the GMO Panel's draft Scientific Opinion from interested parties. This feedback was analyzed, summarized in a report (Devos et al., 2020b), and taken into consideration by EFSA, the expert working group, and the GMO Panel during the revision and completion of the Scientific Opinion (EFSA GMO Panel, 2020). As part of this, answers were provided to the comments received during the online consultation. The public consultation was open from 17th February to 24th April 2020 and received comments from 36 different interested parties/persons, including new actors beyond established participants (Devos et al., 2020b).

A variety of factors influenced how EFSA incorporated engagement into its process to develop the Scientific Opinion. First, for both the expert working group and formal expert testimony there was a tension between achieving the expertise deemed necessary and achieving a gender and geographical balance. Ultimately, EFSA chose to ensure the necessary expertise was present, thereby constraining opportunities for engagement, and indirectly highlighting the importance of how we envision diversity within groups of experts (see Section 4). Second, there was a tension between efficiency and broad inclusion (e.g., with respect to worldviews and breadth of issues considered). Third, and relatedly, there was a choice between: 1) providing the EC a single Scientific Opinion based on the most dominant set of perspectives (or worldview) that emerged during the completed actions; and 2) including within the Scientific Opinion a secondary set of perspectives, not in alignment with the dominant ones, that emerged during the stakeholder workshop and public consultation (Devos et al., 2020b, 2020c). Fourth, there were resource constraints, expertise constraints (e.g., lack of social science expertise), and time constraints that impacted the design of these actions.

3.2. Target Malaria and environmental RA for gene drive mosquitoes

Target Malaria is a not-for-profit research consortium that "aims to develop and share new, cost-effective and sustainable genetic technologies to modify mosquitoes and reduce malaria transmission" (Target Malaria, 2021). Target Malaria is developing suppression gene drives that would complement other control measures (e.g., bednets, insecticide) directed at *Anopheles* malaria vectors affecting countries in West and East Africa. Its research follows a stepwise process (WHO, 2021) that ultimately would lead to the development and deployment of a persistent (i.e., self-sustaining, non-localized) gene drive for managing malaria transmitting mosquitoes. Through these steps, Target Malaria is developing and testing different strains of mosquitoes to design an eventual product strain that achieves intended characteristics of safety, efficacy, sustainability and acceptance.

As a developer, Target Malaria, along with future implementation partners, determines the genetic strain that it would make available for vector control, the environmental release approach proposed for its use, and the expected efficacy targets. Applications for field testing, and many of the steps leading to a final deployment decision, would be subject to a formal RA directed by relevant authorities in the countries involved. The consortium must anticipate the eventual RA requirements and gather appropriate evidence to meet those needs. Target Malaria's gene drive project builds on its experience with previous genetic control technologies such as GM sterile mosquitoes and is concerned with understanding, prioritizing, and investigating potential risks, and preparing for regulatory submissions related to gene drive mosquitoes for environmental release. Specifically, this approach involves four processes: 1) identification of relevant topics of concern and decisions about whether they need additional study, management actions, or communication actions (see Fig. 2); 2) prioritization of scientific studies on topics of concern; 3) conducting and commissioning studies; and 4) identification of topics for inclusion in regulatory submissions and updates (see Fig. 3).

Target Malaria is organized into functional teams related by discipline and into working groups that bring staff from different disciplines together to address specific tasks. There are seven key teams within Target Malaria that take part in RA processes: 1) Science; 2) Risk; 3) Regulatory Affairs; 4) Modelling; 5) Stakeholder Engagement; 6) Communications; and 7) Management. The roles and tasks of each of these team is briefly outlined in Table 1.

The Science Teams represent over half the staff in the consortium, while the Risk, Regulatory and Modelling Teams together are approximately 15 % of the overall project consortium's staff, each representing 5 % of the project staff. The two dedicated Engagement and Communication Teams comprise about 25 % of consortium staff, with the majority in the Stakeholder Engagement Team. Many individuals across these teams work part-time in other roles to foster the cross fertilization of ideas and experiences. Target Malaria also creates cross-cutting ad hoc working groups across the teams as needed. For example, there are working groups on strategy, product development, insectary operations, field studies, and strategic environmental assessment.

A key part of Target Malaria's approach to RA is the ongoing process of identifying relevant topics of concern that need further study, management actions, or communication actions (Fig. 2). There are six routes by which topics of concern are identified and each involves a different type of engagement:

1) Stakeholder Engagement and Communication Teams identify topics of concern from interactions with local communities and stakeholders (including expert and non-expert stakeholders and local and international stakeholders) and from monitoring local and international media sources and meetings;
2) Risk, Science, or Regulatory Teams identify topics of concern during the course of their work or through interactions with peers;

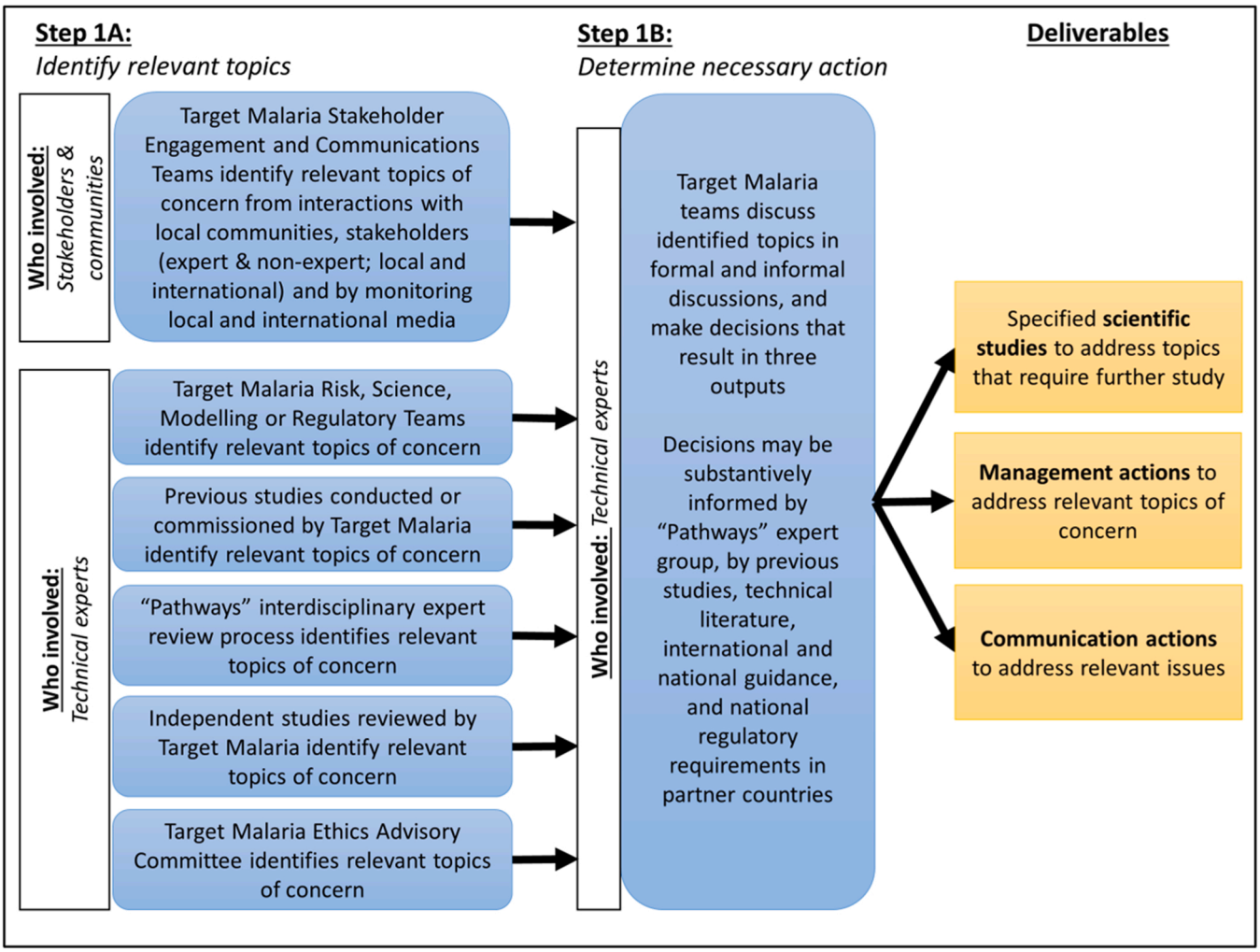

Fig. 2. Target Malaria's first steps to identify relevant topics of concern and initial actions in response. The process is depicted as generally linear and the sources are shown separately to indicate the general flow and function; in practice there is considerable iteration and interaction.

3) Studies conducted or commissioned by Target Malaria identify topics of concern;
4) Interdisciplinary review workshops with internal and external expert participants (e.g. Connolly et al., 2021, 2022) following up topics identified in project initiatives;
5) Independent studies reviewed by Target Malaria teams identify topics of concern;
6) Target Malaria Ethics Advisory Committee can identify areas of concern.

The interdisciplinary expert review (point 4 above) involved an interdisciplinary group of researchers – including social scientists, ethicists and natural scientists – providing feedback (Connolly et al., 2022) on risk pathways previously identified by Target Malaria (Connolly et al., 2021). Target Malaria organized this interdisciplinary review because of its commitment to transparency and because it wanted to efficiently facilitate feedback on the Connolly et al. (2021) "Pathways" paper. Target Malaria chose participants across four key fields of study: ecology, regulation, communication, and modeling. It selected individuals who could commit to all parts of the process and who were not deemed to be categorically opposed to gene drive technology. This approach attempted to demonstrate how the project could articulate pathways related to concerns and get diverse feedback with practical recommendations on how to address them.

Once a topic of concern has been identified, there are then formal and/or informal discussions among project teams and working groups culminating in decisions resulting in three possible outputs (scientific studies, management actions, communication actions) (Fig. 2). These discussions and decisions may be substantively informed by previous studies, existing international and national guidance, national regulatory requirements, or by the interdisciplinary expert review workshops and papers. When specifically considering topics of concern raised by communities and other stakeholders through the Stakeholder Engagement and Communication Teams, some of the criteria that Target Malaria uses for determining whether a topic is added to the list for further study include: How important the topic is to communities and stakeholders, if effective scientific studies can be designed and conducted to investigate the topic, and if the event chain for the concern is deemed scientifically plausible and rational. If a topic is included on the list of scientific studies, that signifies that Target Malaria finds the topic important and feasible to study. There are over 100 scientific studies that are being carried out from this list, with the actual number varying based on how studies are aggregated. Topics on the list include, for example: 1) Would vector competence be different for a gene drive mosquito strain compared to non-gene drive mosquitoes?; and 2) Would the use of a particular gene drive mosquito strain adversely affect any vulnerable ecological trophic networks? Topics are added to and dropped from the list based on changing scientific, ecological and societal contexts. For example, if new scientific findings deem an existing study on the list is no longer relevant, then that study may be removed from

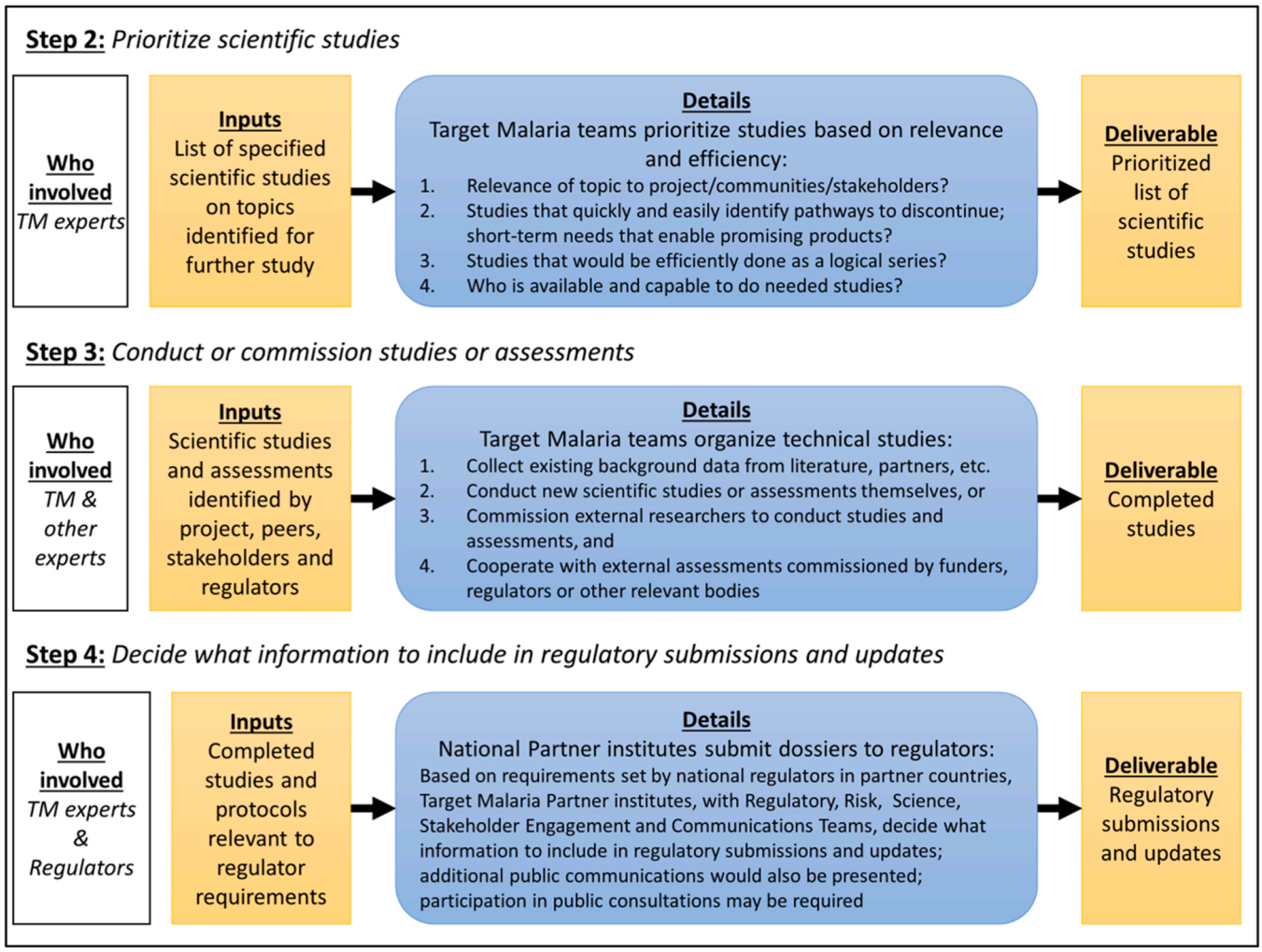

Fig. 3. Target Malaria's second, third and fourth processes to 2] Prioritize scientific studies on topics of concern; 3) Conduct and commission studies; and 4) Identify topics for inclusion in regulatory submissions and updates. These processes focus on the decisions that emerge from the first process, outlined in Fig. 2. The process illustrates a broad sequential process, which involves many different lines of issues proceeding at different rates; there are numerous iterations within the general gathering of evidence.

the list.

Target Malaria's second process involves prioritizing the importance of topics for study and determining the order and location in which the many identified scientific studies should be conducted (Fig. 3). These prioritization decisions are made based on efficiency and practicality criteria. Guiding questions for prioritization include, for example: What studies could most quickly and easily identify strains or potential research products that should be abandoned, before additional effort is wasted on their development? What studies are best conducted together at the same time and location? Who is available to conduct studies (e.g. capacity, skills, cost, etc.)? What studies address the topics of greatest concern to communities, other stakeholders, such as regulators, or Target Malaria team members?

Target Malaria's third process involves conducting or commissioning the necessary studies. The Science Teams perform many of these studies, but Target Malaria also commissions external providers for some studies to draw upon needed expertise and/or serve as an independent quality check. For example, Target Malaria commissioned external researchers to conduct vector competence studies on the GM sterile male strain due to their experience and expertise in conducting routine studies of this type. Independent RAs conducted by Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) on Target Malaria self-limiting sterile male strains (Hayes et al., 2015) have been carried out during earlier stages in the stepwise development pathway, and similar independent RAs are expected to inform future applications leading to gene drive mosquitoes.

Target Malaria's fourth process involves identifying information to include in regulatory submissions and updates. Regulatory submissions will be made by Target Malaria national partner institutions, using data from the consortium and external sources. These decisions are primarily informed by the regulatory mandates in the African countries where Target Malaria works. Target Malaria, including its national partners, works with regulators on all actions relevant to regulatory approval, keeping regulators informed in general about what is being done and responding to specific queries as they arise. Actions that require regulatory approval vary from creating contained use facilities for testing, to releasing non-gene drive GM sterile male strain mosquitoes into the environment, to ultimately releasing a particular strain of gene drive mosquitoes into the environment. In any future regulatory application for the environmental release of gene drive mosquitoes, Target Malaria and its national partner institutions will make decisions about what materials to include within the application in consultation with and at the direction of national regulators and/or their independent risk assessors. As developers and potential applicants, Target Malaria and its partners need to be able to communicate their intended plans effectively to regulators and other relevant parties in study or release scenarios in which it can be shown that evidence addresses each clearly identified pathway to harm. While regulators must interpret what data is needed

Table 1
Description of Target Malaria's Teams.

Team	Description
Science	Includes a broad group of over 100 geneticists and ecologists with expertise in molecular and synthetic biology and ecology. They are charged with developing the gene drive technology in the laboratory and establishing background ecology and genetics in the field. These experts are organized in clusters across numerous institutions in multiple countries, with many working on gene drive along with other complementary academic roles.
Risk	Addresses issues related to risk and product performance across the project and includes individuals with expertise in RA and risk management, standard practices and audit, risk modelling, and information management.
Regulatory Affairs	Responsible for preparing evidence for regulatory submission and includes individuals with expertise in the technology, dossier management, identifying regulatory science requirements, and compliance management.
Modelling	Addresses fundamental and applied questions related to spatial and temporal dynamics of gene drive persistence, spread and impact.
Stakeholder Engagement	Responsible for opening and maintaining dialogue with stakeholders at local, regional and national levels to ensure project understands stakeholder views, listens to concerns and integrates these perspectives in project development.
Communications	Includes communication experts who track and contribute to relevant media coverage, and communicate the purpose, science, and implications of Target Malaria's different projects.
Management	Coordinates all activities, relates tasks to milestones and project deliverables, and liaises with funders and partner institutions.

for an effective RA, developers should be contributing to that process by describing how evidence on their intended applications is relevant to perceived potential risks. This also allows other stakeholders to provide additional evidence and viewpoints relevant to the protection goals addressed by national regulatory authorities.

A variety of factors influence how Target Malaria involves stakeholders across these four processes. One factor involves the very definition of stakeholder. For example, the Stakeholder Engagement Team largely focuses on local stakeholders, communities near insectaries or release sites, national authorities, and the general public. Target Malaria also, however, defines scientific peers and regulators as stakeholders that should be engaged in its RA activities. In this way, the Stakeholder Engagement Team engages with some stakeholders, while other groups within Target Malaria may involve other stakeholders. In addition, there is overlap across teams on engagement: for example, one of the Stakeholder Engagement Team leaders had a major part in the Pathways interdisciplinary expert review process, and individuals from the Science Teams work with the Stakeholder Engagement Team on interpreting concerns and acquired knowledge, and with the Communication Team on messaging in response to concerns. This engagement informs and learns from the wider context of project engagement. Another factor impacting how Target Malaria involves stakeholders is in the criteria the project uses to identify which topics of concern identified by stakeholders are relevant for additional study. Target Malaria decides what is a scientifically rational and plausible topic and therefore potentially worthy of additional study. This is a consequential judgment that impacts whether and how stakeholders are involved, if indirectly, in determining topics for further scientific study.

4. Reflections on engagement on risk assessment by EFSA and Target Malaria

Three principal reflections emerged from this work. First, gene drive RA is not simply concerned with a technology developer's preparation of an application for use, including evidence for a formal RA, and its review by a risk assessor. Instead, it involves multiple processes and decisions in different forms across the entire technology and regulatory development process. Although they share an interest in assessing the risks of gene drive insects, EFSA and Target Malaria actions are driven by their very different roles within the RA process. EFSA is a risk assessor following a given mandate to assess specific product and use applications. In this role, it reviewed the adequacy and sufficiency of existing RA guidelines using an expert working group, a stakeholder workshop, expert testimony, and an online public consultation on its draft findings. Target Malaria is a research consortium developing gene drive mosquitoes and so explores a broader range of RA-related questions along multiple product development routes with a process that includes, for example: identifying topics of concern for additional study, selecting which topics to study and in what order, conducting or commissioning studies, and anticipating what information is required for regulatory submissions. EFSA and Target Malaria are engaging with academic, stakeholder experts, and publics to ensure their respective roles and processes are effective. For EFSA, the evaluation of the Scientific Opinion proceeded in a more-or-less linear fashion, while Target Malaria's approach has been more iterative and integrated into its technology development process. In both cases, these are the first steps on a longer journey.

Second, EFSA and Target Malaria both integrated engagement into their respective approaches, recognizing the need for engagement on various decisions and incorporating it in some novel ways. For example, EFSA used a stakeholder workshop to obtain a broader set of views about gene drive risks (Devos et al., 2020c) – something it does not normally do. Target Malaria incorporated engagement in multiple ways, with different actors and for distinct purposes. Target Malaria's Stakeholder Engagement, Communication, Science, Risk and Regulatory Affairs Teams all engage with their respective peers and others in the assessment of risk. These efforts are directed towards an effective and efficient process of creating a product with appropriate performance and safety characteristics. Target Malaria has recently taken a novel step in publishing its investigation of potential pathways to harm, part of the problem formulation stage of RA (Connolly et al., 2021). In addition to its Stakeholder Engagement Team helping to identify topics of concern at community and national levels, the project also designed an interdisciplinary expert review process to elicit feedback on its risk-related work (see Connolly et al., 2022). This has opened up this stage of RA more than has often been the case in biotechnology development and gives the consortium an opportunity to learn further from academic, public and other stakeholder responses to the scenarios, structures, logic and evidence needs.

EFSA and Target Malaria also pursued engagement in different ways, reflecting their different roles and purposes. EFSA is a public agency required to follow consistent processes related to both how it conducts RA and engagement. It followed its normal technically-driven process to assess the adequacy and sufficiency of its existing GMO RA guidelines for gene drive technologies when there was a formal mandate to do so from the EC. Each of the stakeholder and public engagement steps it took (stakeholder workshop and online consultation) required different types of deliberations and agreements within EFSA or the EC. Target Malaria, as a gene drive product developer, is constrained by the need to prepare application dossiers with technical evidence that can be reviewed by regulators. However, as an independent, non-profit research consortium largely set in academia, it has many options in deciding how it prepares that risk evidence and who it wants to involve. As a result, it has greater flexibility in its processes, including how it incorporates different types of engagement (from communities and other stakeholders), to prepare for the formal stage of RA carried out or commissioned independently by a regulator.

Third, while EFSA and Target Malaria have demonstrated different and novel ways to incorporate engagement, there may still be opportunities to learn from these and strengthen future engagement efforts. To understand how, it is helpful to think about engagement in terms of democratic and epistemic rationales. Democratically motivated engagement concerns actions taken to achieve basic democratic norms

such as transparency and the ability for stakeholders and the public to inform and participate in decisions. Epistemically motivated engagement concerns actions taken to ensure that the production of knowledge is relevant, rigorous and robust (NASEM, 2016; Stirling, 2008).

EFSA's process involved engagement that was democratically and epistemically motivated. Democratic motivations focused on ensuring stakeholders and the public have a chance both to name risks they are concerned about, and to review draft documents. The stakeholder workshop and online public consultation successfully involved new stakeholders, helped identify risks of concern, and helped map the divergence of views on this issue. The stakeholder workshop ultimately fell short of its full potential to contribute epistemically by substantively informing problem formulation for reasons discussed in Section 3.1. Interestingly, the selection of members of the expert working group is also concerned with broadening epistemic inputs, yet this selection was not viewed as a form of engagement by EFSA.

Target Malaria engagement activities span both democratic and epistemic dimensions. The Stakeholder Engagement and Communication Teams, which reach out to local communities and other stakeholders, are both democratically and epistemically motivated. The primary aims of engagement are ensuring transparency and enabling communities and stakeholders to have a chance to identify concerns they might have about the technology. However, the engagement captured by Target Malaria's expert pathway review panel is more clearly epistemic in nature, seeking to include a breadth of interdisciplinary views with participants selected for their knowledge. It followed up on its publication of the potential pathways to harm with a series of expert workshops with ecologists, regulatory scientists and social scientists. Such engagement enables Target Malaria to test assumptions about what people in these communities know and value. Both case studies show the importance of recognizing and fostering democratic and epistemic engagement on RA processes for environmental releases of gene drive insects. These case studies also show that the form democratic and epistemic engagement take will be different based on the specific constraints and opportunities facing differently situated organizations.

Epistemic engagement involving experts requires strengthening the traditional focus on disciplinary diversity, but also broadening engagement to include worldview diversity, which might include experts in the same discipline who hold different worldviews. This need emerges from the realization that people who share expertise in a particular discipline may make RA-related decisions differently based on their risk tolerance (e.g., risk seeking or risk averse), relationship to nature (e.g., exploitative, utilitarian, caretaking), relationship to technology (e.g., technological optimist, agnostic, critic), and relationship to governmental regulation (e.g., type and degree of governmental regulation required for societally beneficial technology to be developed) (Flint et al., 2013; Holifield, 2012; Whyte et al., 2016). These forms of diversity may impact the problem formulation step of RA (e.g., how one defines specific or operational protection goals, relevant adverse effects, and needed studies) as well as other parts of RA (e.g., how extrapolations are made, levels of acceptable uncertainty, how studies are designed, conducted, and interpreted, and how conflicting studies are reconciled) (Hartley and Kokotovich, 2018; Jensen et al., 2003; Kuzma, 2019; Thompson, 2003). For example, if members of an interdisciplinary group are risk-seeking, technological optimists that view nature as something to be exploited by humans and believe in the unregulated free market (or risk averse, protective of nature, stringent regulation supporting, technological critics), then that will affect how they make risk-related decisions. Considering disciplinary diversity *and* worldview diversity helps avoid slipping into the idea that worldview diversity is something only held by stakeholders and the public, but not experts. Diversity both between and within disciplines will help to ensure that important decisions, and the assumptions informing them, are subject to adequate scrutiny.

Risk assessors and technology developers should foster both disciplinary and worldview diversity when planning and conducting epistemically motivated engagement. For example, if risk assessors brought both disciplinary and worldview diversity considerations into the selection of their working group experts, such as EFSA's gene drive expert working group, they might address the concerns from critics about the narrow range of expertise shaping RA (Corporate Europe Observatory, 2019). EFSA's future work on RA guidelines could be strengthened by emphasizing the role of disciplinary and worldview diversity in its engagement and involvement of experts in its working groups. Broadening epistemic input at EFSA could start immediately with diversifying the range of hearing experts providing testimony to expert working group meetings. Broadening the disciplinary and worldview diversity of the expert working group may take more time and may face resistance from those who insist that the selection of experts does not require consideration of worldviews. While Target Malaria demonstrates its desire to gather a broad range of inputs, it could, in the future, explicitly consider the breadth of diversity within the disciplines, as well as the range of disciplines engaged. Target Malaria and EFSA each have conducted various engagement efforts that reflect disciplinary diversity but it is less clear whether worldview diversity is reflected. This may require guidance on how to judge worldview diversity within relevant disciplines. More explicit recognition of the value of diverse inputs and the way in which those inputs influence processes and evidence for RAs may encourage greater and more effective participation.

This collaborative work has implications for engagement on gene drive RA beyond the mosquito case discussed here. First, existing scholarship on engagement on RA has tended to focus on engagement on the problem formulation stage of formal RA, yet the two cases show that there are many RA-related decisions and processes leading up to formal RA for gene drive technologies and that engagement can have a role in all of them. These findings support a broadening of how engagement on RA is envisioned and pursued. Second, and relatedly, in broadening how engagement on RA is envisioned, these cases also invite a broadening of the types of methods used for engagement on RA. There is a breadth of possible methods that can be used to support engagement on RA including focus groups, interviews, surveys and consensus conferences (Rowe and Frewer, 2005), which complement current activities. Encouraging participation from social scientists in the range of risk decisions that have been highlighted in these two cases can help identify and develop additional engagement methods. Third, for risk assessors and regulatory agencies, a focus on democratic engagement may mask opportunities for broadening epistemic inputs. In such situations, it is important to consider not just disciplinary diversity in the selection of experts, but also worldview diversity – including the diversity that exists within a discipline. There are practical challenges to this approach, particularly for risk assessors and regulatory agencies, and a first step might be to review selection criteria for working group participation (members and hearing experts) and seek new networks to identify suitable experts. Smith et al. (2021) offer a method to identify participants for engagement that reaches beyond traditional and familiar networks and emphasizes the role of participants as knowledge-holders. It is important for efforts seeking to broaden worldview diversity to explicitly reflect on how worldviews differ and what is at stake in such differences. Finally, EFSA and Target Malaria have explicit commitments to transparency. Such transparency can be an important first step in engagement, by helping to make clear what decisions are being made and the potential role of engagement in them. Demonstrating the processes leading to RAs and the attention to engagement in the two cases is an important step in opening up these often highly technical spaces.

Disclaimer

The views expressed in this publication are those of the authors and should not be interpreted as representing the official position of the European Food Safety Authority (EFSA). EFSA assumes no responsibility

or liability for any errors or inaccuracies that may appear. Similarly, the representation of the processes within Target Malaria are from the perspective of the authors.

Memorial

In our professional lives, we have the privilege to meet extraordinary and unique people who pass on their passion for science, shape your way of thinking, and inspire you. John Mumford is one of them – a brilliant and highly esteemed scientist, and an exceptionally generous, warm, gentle and humble soul. While working on this manuscript/project together, we have been struck – once more – by: John's clarity of thought, both verbally and in writing; his ability to look at complex issues, separate them into understandable pieces, and explain them in an orderly, useful and engaging way; his respect to others, irrespective of their ideas; and his drive to share knowledge, be helpful and teach. Sadly, John left us far too early, leaving behind an extremely impactful legacy in his scientific field. Our sincere condolences to his family and friends for the loss of a wonderful, gracious man.

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CRediT authorship contribution statement

YD and JM initiated the collaboration with SH. SH and AK conceptually framed the paper with feedback from YD and JM. All authors took part in collaborative meetings. Working closely with SH, AK drafted the paper based on these meetings with iterative, substantive feedback from SH, YD, and JM. SH and AK made multiple and extensive revisions to various drafts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Connolly, J.B., Mumford, J.D., Fuchs, S., Turner, G., Beech, C., North, A.R., Burt, A., 2021. Systematic identification of plausible pathways to potential harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector Anopheles gambiae in West Africa. Malar. J. 20, 170. https://doi.org/10.1186/s12936-021-03674-6.

Connolly, J.B., Mumford, J.D., Glandorf, D.C.M., Hartley, S., Lewis, O.T., Evans, S.W., Turner, G., Beech, C., Sykes, N., Coulibaly, M.B., Romeis, J., Teem, J.L., Tonui, W., Lovett, B., Mankad, A., Mnzava, A., Fuchs, S., Hackett, T.D., Landis, W.G., Marshall, J.M., Aboagye-Antwi, F., 2022. Recommendations for environmental risk assessment of gene drive applications for malaria vector control. Malar. J. 21, 152. https://doi.org/10.1186/s12936-022-04183-w.

Corporate Europe Observatory, 2019. EFSA gene drive working group fails independence test. URL https://corporateeurope.org/en/2019/06/efsa-gene-drive-working-group-fails-independence-test (accessed 12.2.21).

Delborne, J., Kuzma, J., Gould, F., Frow, E., Leitschuh, C., Sudweeks, J., 2018. Mapping research and governance needs for gene drives. S4–S12 J. Responsible Innov. 5. https://doi.org/10.1080/23299460.2017.1419413.

Devos, Y., Bonsall, M.B., Firbank, L.G., Mumford, J., Nogué, F., Wimmer, E.A., 2020a. Gene drive-modified organisms: developing practical risk assessment guidance. Trends Biotechnol. 39, 853–856. https://doi.org/10.1016/j.tibtech.2020.11.015.

Devos, Y., Bonsall, M.B., Nogué, F., Paraskevopoulos, K., Wimmer, E.A., Firbank, L.G., 2020b. Outcome of a public consultation on the draft adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA Support. Publ. 17, 1939E. https://doi.org/10.2903/sp.efsa.2020.EN-1939.

Devos, Y., Gallani, B., Firbank, L.G., 2020c. Stakeholder workshop "Problem formulation for the environmental risk assessment of gene drive modified insects" (15 May 2019, Brussels). EFSA Support. Publ. 17, 1819E. https://doi.org/10.2903/sp.efsa.2020.EN-1819.

Devos, Y., Mumford, J.D., Bonsall, M.B., Camargo, A.M., Firbank, L.G., Glandorf, D.C.M., Nogué, F., Paraskevopoulos, K., Wimmer, E.A., 2021a. Potential use of gene drive modified insects against disease vectors, agricultural pests and invasive species poses new challenges for risk assessment. Crit. Rev. Biotechnol. 0, 1–17. https://doi.org/10.1080/07388551.2021.1933891.

Devos, Y., Mumford, J.D., Bonsall, M.B., Glandorf, D.C.M., Quemada, H.D., 2021b. Risk management recommendations for environmental releases of gene drive modified insects. Biotechnol. Adv., 107807 https://doi.org/10.1016/j.biotechadv.2021.107807.

EFSA, 2018. EFSA rules on competing interest management.

EFSA, 2021. Genetically Modified Organisms [WWW Document]. URL https://www.efsa.europa.eu/en/science/scientific-committee-and-panels/gmo (accessed 9.23.21).

EFSA, 2022. Values [WWW Document]. URL https://www.efsa.europa.eu/en/about/values (accessed 4.3.22).

EFSA GMO Panel, 2013. Guidance on the environmental risk assessment of genetically modified animals. EFSA J. 11, 3200. https://doi.org/10.2903/j.efsa.2013.3200.

EFSA GMO Panel, 2020. Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. e06297 EFSA J. 18. https://doi.org/10.2903/j.efsa.2020.6297.

Flint, C.G., Kunze, I., Muhar, A., Yoshida, Y., Penker, M., 2013. Exploring empirical typologies of human–nature relationships and linkages to the ecosystem services concept. Landsc. Urban Plan. 120, 208–217. https://doi.org/10.1016/j.landurbplan.2013.09.002.

Flyvbjerg, B., 2006. Five misunderstandings about case-study research. Qual. Inq. 12, 219–245. https://doi.org/10.1177/1077800405284363.

Foote, N., 2020. NGOs call for moratorium on controversial "gene drive organisms." www.euractiv.com.

Hartley, S., 2016. Policy masquerading as science: an examination of non-state actor involvement in European risk assessment policy for genetically modified animals. J. Eur. Public Policy 23, 276–295. https://doi.org/10.1080/13501763.2015.1049196.

Hartley, S., Kokotovich, A., 2018. Disentangling risk assessment: New roles for experts and publics. In: Nerlich, B., Hartley, S., Raman, S., Smith, A. (Eds.), Here Be Monsters: Science, Politics and the Dilemmas of Openness. Manchester University Press, Manchester, England, pp. 176–194.

Hartley, S., Kokotovich, A., McCalman, C., 2022. Prescribing engagement in environmental risk assessment for gene drive technology Regulation and Governance.

Hayes, K.R., Barry, S., Beebe, N., Dambacher, J.M., Barro, P.D., Ferson, S., Ford, J., Foster, S., Goncalves da Silva, A., Hosack, G.R., 2015. Risk assessment for controlling mosquito vectors with engineered nucleases: sterile male construct final report. CSIRO.

Holifield, R., 2012. Environmental justice as recognition and participation in risk assessment: negotiating and translating health risk at a superfund site in Indian country. Ann. Assoc. Am. Geogr. 102, 591–613.

Interdisciplinary Workshop on Synthetic Gene Drives [WWW Document], 2021. URL https://flodebarre.github.io/genedrive2021/ (accessed 12.13.21).

Jensen, K.K., Gamborg, C., Madsen, K.H., Jorgensen, R.B., Krauss, M.K., Folker, A.P., Sandoe, P., 2003. Making the EU "Risk Window" transparent: the normative foundations of the environmental risk assessment of GMOs. Environ. Biosaf. Res. 2, 161–171.

Keiper, F., Atanassova, A., 2020. Regulation of synthetic biology: developments under the convention on biological diversity and its protocols. Front. Bioeng. Biotechnol. 310.

Kokotovich, A.E., Delborne, J.A., Elsensohn, J., Burrack, H., 2020. Emerging technologies for invasive insects: the role of engagement. Ann. Entomol. Soc. Am. 113, 266–279. https://doi.org/10.1093/aesa/saz064.

Kokotovich, A.E., Barnhill-Dilling, S.K., Elsensohn, J.E., Li, R., Delborne, J.A., Burrack, H., 2022. Stakeholder engagement to inform the risk assessment and governance of gene drive technology to manage spotted-wing drosophila. J. Environ. Manag. 307, 114480 https://doi.org/10.1016/j.jenvman.2022.114480.

Kuzma, J., 2019. Procedurally robust risk assessment framework for novel genetically engineered organisms and gene drives: risk assessment for GEOs and gene drives. Regul. Gov. https://doi.org/10.1111/rego.12245.

Ledingham, K., Hartley, S., 2021. Transformation and slippage in co-production ambitions for global technology development: the case of gene drive. Environ Sci Policy 116, 78–85.

Long, K.C., Alphey, L., Annas, G.J., Bloss, C.S., Campbell, K.J., Champer, J., Chen, C.-H., Choudhary, A., Church, G.M., Collins, J.P., Cooper, K.L., Delborne, J.A., Edwards, O. R., Emerson, C.I., Esvelt, K., Evans, S.W., Friedman, R.M., Gantz, V.M., Gould, F., Hartley, S., Heitman, E., Hemingway, J., Kanuka, H., Kuzma, J., Lavery, J.V., Lee, Y., Lorenzen, M., Lunshof, J.E., Marshall, J.M., Messer, P.W., Montell, C., Oye, K.A., Palmer, M.J., Papathanos, P.A., Paradkar, P.N., Piaggio, A.J., Rasgon, J.L., Rašić, G., Rudenko, L., Saah, J.R., Scott, M.J., Sutton, J.T., Vorsino, A.E., Akbari, O.S., 2020. Core commitments for field trials of gene drive organisms. Science 370, 1417–1419. https://doi.org/10.1126/science.abd1908.

NASEM, 2016. Gene Drives on the Horizon: Advancing Science: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. National Academies Press,.
Roberts, A.J., Thizy, D., 2022. Articulating ethical principles guiding Target Malaria's engagement strategy. Malar. J. 21, 35. https://doi.org/10.1186/s12936-022-04062-4.
Rod, M.R.M., Paliwoda, S.J., 2003. Multi-sector collaboration: a stakeholder perspective on a government, industry and university collaborative venture. Sci. Public Policy 30, 273–284. https://doi.org/10.3152/147154303781780399.
Rodríguez-Campos, L., 2012. Advances in collaborative evaluation. Eval. Program Plann., Collab. Eval.: Theory Pract. 35, 523–528. https://doi.org/10.1016/j.evalprogplan.2011.12.006.
Rowe, G., Frewer, L.J., 2005. A typology of public engagement mechanisms. Sci. Technol. Hum. Values 30, 251–290.
Smith, R.D.J., Hartley, S., Jewitt, T., Middleton, P., 2021. Knowing when to talk? Plant genome editing as a sitefor pre-engagement institutional reflexivity. Public Underst. Sci. 30 (6), 740–758.
Steen, M., 2021. Slow Innovation: the need for reflexivity in Responsible Innovation (RI). J. Responsible Innov. 0, 1–7. https://doi.org/10.1080/23299460.2021.1904346.
Stirling, A., 2008. "Opening Up" and "Closing Down": power, participation, and pluralism in the social appraisal of technology. Sci. Technol. Hum. Values 33, 262–294.
Stirling, A., Hayes, K.R., Delborne, J., 2018. Towards inclusive social appraisal: risk, participation and democracy in governance of synthetic biology. BMC Proc. 12, 15. https://doi.org/10.1186/s12919-018-0111-3.
Target Malaria, 2021. Who We Are [WWW Document]. Target Malar. URL https://targetmalaria.org/about-us/who-we-are/ (accessed 11.11.21).
Thompson, P.B., 2003. Value judgments and risk comparisons. the case of genetically engineered crops. Plant Physiol. 132, 10–16.
WHO, 2021. Guidance framework for testing of genetically modified mosquitoes, second edition. World Health Organization, Geneva.
Whyte, K.P., Brewer, J.P., Johnson, J.T., 2016. Weaving Indigenous science, protocols and sustainability science. Sustain. Sci. 11, 25–32. https://doi.org/10.1007/s11625-015-0296-6.
Wickson, F., Wynne, B., 2012. The anglerfish deception. EMBO Rep. 13, 100–105.
Zwart, H., Nelis, A., 2009. What is ELSA genomics? EMBO Rep. 10, 540–544. https://doi.org/10.1038/embor.2009.115.