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Convention on Biological Diversity

Multidisciplinary Ad Hoc Technical Expert Group on Synthetic Biology to Support the Process for Broad and Regular Horizon Scanning, Monitoring and Assessment
Second meeting
Montreal, Canada, 29 January–2 February 2024
Item 3 of the provisional agenda*
Implementation of the mandate

Prioritized list of trends and issues in synthetic biology

Note by the Secretariat**

I. Introduction

1. The multidisciplinary Ad Hoc Technical Expert Group on Synthetic Biology ("multidisciplinary Expert Group") at their meeting in July 2023 agreed on a process for the first cycle of broad and regular horizon scanning, monitoring and assessment of the most recent technological developments in synthetic biology. The process for the 2023-2024 intersessional period consisted of both multidisciplinary expert-driven submissions by members of the multidisciplinary Expert Group and a literature review conducted by the Secretariat.

2. In line with the request from the multidisciplinary Expert Group, the Secretariat produced a revised list of issues and trends of synthetic biology ("the provisional selection list") based on the 2019 report of the Ad Hoc Technical Expert Group on Synthetic Biology (CBD/SYNBIO/AHTEG/2019/1/3), the Open-ended Online Forum on Synthetic Biology convened from 20 to 31 March 2023, the submissions of information in response to notification No. 2023-006 and the publication "Technical Series No. 100: Synthetic Biology".

3. Following the compilation of the provisional selection list, the members of the multidisciplinary Expert Group were invited to select up to five items from the list or submit new items for consideration that in their expert opinion would be the most prominent issues to consider for the first cycle of broad and regular horizon scanning, monitoring and assessment using an electronic submission form. In performing their selection, the experts were requested to provide information on the potential impacts on the three objectives of the Convention on Biological Diversity, additional relevant considerations (e.g., socioeconomic, cultural or ethical), the estimated timeframe for release or impact of the selected item and relevant documentation to support their selection. Submissions were received from 31 August until 18 September 2023.

4. At their virtual meeting from 10 to 13 October 2023, the members of the multidisciplinary Expert Group prioritized a list of 17 trends and issues in synthetic biology for assessment at the next

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** The present document has been issued without formal editing.

physical meeting of the multidisciplinary Expert Group. Five of these items were selected for a detailed assessment (section II) and the other twelve were recommended for a less detailed assessment (section III).

5. To further support their assessment, an additional submissions of information process occurred to support the 12 items for a less detailed assessment and an additional round of online discussions of the Open-ended Online Forum on Synthetic Biology were held from 6 to 22 November 2023 to gather supplementary information for the 5 items for a detailed assessment.

6. This present document represents a compilation of the multidisciplinary expert-driven submission process, including the submissions of information and a summary of the Open-ended Online Forum on Synthetic Biology. Each of the 17 items on the prioritized list are detailed below, with the 5 items for a detailed assessment contained in section II and the 12 items for a less detailed assessment are contained in section III. All bibliographic references shared during the process can be found in the annex.

II. Trends and issues identified for detailed assessment

A. Self-spreading vaccines for wildlife

7. Self-spreading vaccines for wildlife are designed to either limit the spread of wildlife diseases or to viral vector-mediated immunocontraception to reduce target animal population sizes. These approaches generally involve engineered live viruses or viral vectors designed to spread through a wildlife population to confer resistance to a particular pathogen. In some cases, non-replicating viral vectors are engineered to re-confer vector replication and spread between hosts. These applications can be considered to be "*living modified organisms*" (LMOs) according to the Cartagena Protocol on Biosafety.

8. Some specific examples include:

- Modified cytomegalovirus from Natal multimammate mice (*Mastomys natalensis*) to confer immunity to Lassa fever in rodents;
- Modified *Desmodus rotundus betaherpesvirus* targeting Rabies virus in vampire bat populations to prevent the transmission of Rabies to humans in Central and South America;
- Raccoon pox virus vector targeting *Pseudogymnoascus destructans* pathogens in bat populations;
- Transmissible vaccines to control Lassa fever in apes; and
- Self-spreading vaccines to control Ebola virus in monkeys and bats.

1. Timeframe

9. Regarding developments within self-spreading vaccines for wildlife, research and development is currently focused on application to limit wildlife disease or zoonotic spill-over, rather than immunocontraception for population control due to efficacy and delivery challenges identified in early research.

10. The timeframe for release of self-spreading vaccines could be less than five years, noting that one trial in the United States occurred in 2019 for the modified raccoon pox virus vector targeting *Pseudogymnoascus destructans*. There is research in the United States of America and the United Kingdom of Great Britain and Northern Ireland aiming at developing living modified viruses for deployment in South America and West Africa, targeting rabies in bats and Lassa fever in rodents. Further, it was suggested that the technology exists to allow for the accelerated development of vaccines, as demonstrated by the COVID-19 public health crisis.

2. Potential impacts on the objectives of the Convention of Biological Diversity

11. Self-spreading vaccines for wildlife could have both potential positive and potential negative impacts on the three objectives of the Convention on Biological Diversity.

12. Regarding the potential positive impacts on the objectives of the Convention, some could include:

- Immunization of wildlife against pathogen to control disease spread, improving resilience of threatened or naïve populations and/or ecosystems;
- Improved wildlife vaccination in difficult to access areas; and
- Management of pest species and control of invasive alien species.

13. Regarding the potential negative impacts on the objectives of the Convention, some could include:

- Wide host specificity for some viruses may lead to spill-over into non-target hosts (e.g., poxviruses);
- Viral vector evolution (e.g., changes to virulence and infectivity)
- Population reductions of animals in areas of origin in the case of sterilization applications;
- Pathogen response to vaccine (e.g., expanded tissue or host range);
- Lack of stability of modified viruses (e.g., viral evolution, recombination, reversion to parental vector);
- Genotoxic effects (e.g., from horizontal gene transfer or recombination events);
- Immunomodulatory and oncogenic effects;
- Rapid spread depending on viral vector;
- Irretrievability of released; and
- Unpredictable effects on physiological and ecosystem dynamics (e.g., unexpected virulence).

3. Potential gaps to risk assessment, risk management and regulation and availability of tools for detection, identification and monitoring

14. Due to the characteristics of self-spreading vaccines, there could be further considerations that may need to be taken into account for risk assessment, risk management and regulation of these applications. Some potential factors could include:

- Uncertainty in viral evolution (e.g., mutations, vector integrity) and response of modified virus in varying environmental conditions;
- Capacity for superinfection for some viral species;
- Lack of predictability of immune efficacy and side effects during transmission;
- Large or unlimited spatio-temporal distributions (e.g., latency, persistence in environment, spread in unmanaged areas);
- Increased potential for transboundary movements;
- Stepwise testing may not be feasible due unintended spread;
- Lack of risk management options (e.g., irreversibility of release, persistence);
- Limited capacity of developing nations to mange unintended outcomes;
- Long-term and robust monitoring and surveillance systems (e.g., for tracking mutations and unintended impacts of release, viral dynamics in asymptomatic populations, feasibility of such systems);

- Difficulties detecting accidental releases (e.g., in the of spread and persistence of certain vectors in animals);
- Management of safety standards considering they may come into contact with multiple species and potentially humans;
- Need for on-going and flexible risk assessment approaches and regulatory systems to take into account new developments post-release (e.g., changing environmental conditions, new environments, mutations and both intended and unintended responses by the target organisms);
- Limited available guidance materials (e.g., most vaccine guidance is focused on clinical applications for human populations); and
- Need to strengthen regulation in all jurisdictions.

15. In comparison to some of the other technologies and applications being discussed under the auspices of the Convention on Biological Diversity, regulation for such vaccines might be less developed and frameworks for assessing the sustainability of these specific applications are non-existent. Likely, strong cooperation and collaboration between countries and institutions would be required for releases, as well as special consideration of the precautionary principle. However, research programmes were being managed responsibly by the scientists involved.

4. Limits of knowledge

16. Further areas, particularly related to viral biology, may necessitate further exploration based on the available research and data to date. Thus, some potential gaps in knowledge could include:

- Viral evolution and co-evolution with host post-release (e.g., mutations, reversion to parental vector);
- Pathogen response to the intervention (e.g., pathogen evolution);
- Interaction of modified virus with non-target populations (e.g., other species and humans);
- Spatiotemporal scaling of applications (e.g., protection over time, spread dynamics through a target population with respect to previous immunity, superinfection, age, nutritional status, among others);
- Immune system functioning in both target and non-target organisms (e.g., intended immune response, partial or full immunity, chronic exposure);
- Development of adaptive immunity;
- Selective pressure (e.g., selection for mutants with higher dissemination potential or increased virulence);
- Next-generation effects;
- Capacity for superinfection and co-infection dynamics;
- Lack of baseline ecosystem and biological data; and
- Difficulties constructing accurate models.

5. Additional relevant considerations

17. Further to the potential impacts on the three objectives of the Convention, self-spreading vaccines for wildlife could raise additional relevant considerations. Some of these considerations could potentially include:

- Human health (e.g., prevention of zoonotic disease spill-over into human populations and pandemics);

- Alleviate economic costs of affected populations and societies;
- Consideration of the social, political and commercial determinants of health;
- Comparison to alternative interventions;
- Potential biosecurity risks, including misuse and accidental release;
- Access to technology (e.g., intellectual property rights impeding equitable access to the benefits);
- Sustainability of the intervention (e.g., not addressing root cause of disease such as human encroachment on wildlife areas and climate change, high costs, efficacy of application over time);
- Need to consider liability and redress prior to release;
- Free, prior and informed consent of potentially affected indigenous peoples and local communities;
- Ethics (e.g., human intervention in nature, existing human influence on ecosystems, worldview of indigenous peoples and local communities);
- Co-implementation with traditional conservation methods (e.g., over reliance on technological solutions);
- Potential for issue to be conflated with human vaccine hesitation and opposition (e.g., misinformation);
- Stakeholder and public engagement in decision-making (e.g., full and effective participation);
- Public awareness and acceptance (e.g., changes in risk aversion);
- Transparency and access to information (e.g., timely publication of regulatory documents and scientific publications); and
- Differences in the locations of development and deployment of these applications.

6. Potential lessons from other domains

18. Regarding potential lessons that could be applied to the consideration of self-spreading vaccines, the sources of applicable information could come from historical biological control interventions. However, experience with other living modified vaccines for veterinary use, other applications designed to spread (e.g., LMOs containing engineered gene drives) and invasive species could also be important and inform assessment of self-spreading vaccines. Further, recent immunological studies could provide insights in to host immune responses.

B. Development of engineered gene drives to control vector-borne diseases and invasive species

19. Engineered gene drives are molecular mechanisms that are transmitted to progeny at super-Mendelian (>50%) frequencies. There are various types of engineered gene drives, but many utilize CRISPR-Cas. Other mechanisms can include toxin-antidote systems and endonucleases, among others. Depending on the system implemented, engineered gene drives can be designed to have an intended wide or localized spread. In certain cases, engineered gene drive mechanisms can be considered to be self-limiting in nature as well.

20. Applications of engineered gene drives can be designed to suppress vectors of human and animal disease, as well as to control invasive species. These are designed as alternative vector-control measures to conventional insecticide or rodenticide applications. Specific applications include:

- Living modified *Anopheles gambiae* containing an engineered gene drive designed to target *doublesex* to reduce malaria transmission;

- Living modified *An. gambiae* containing an endonuclease targeting the X-chromosome;
- Living modified *Aedes aegyptii* to reduce malaria transmission;
- Living modified *Culex sp*. mosquitoes to control West Nile virus transmission;
- Living modified *Drosophila suzukii* for use in fruit orchards; and
- Engineered gene drive rodents to control invasions on islands.

21. Further, LMOs containing engineered gene drives could potentially impact Targets 6 (Reduce the introduction of invasive alien species by 50% and minimize their impact), 7 (Reduce pollution to levels that are not harmful to biodiversity) and 20 (Strengthen capacity-building, technology transfer and scientific and technical cooperation for biodiversity) of the Kunming-Montreal Global Diversity Framework. Furthermore, LMOs containing engineered gene drives may also impact the United Nations Sustainable Development Goals 1 (No Poverty), 3 (Good Health and Well-being), 5 (Gender Equality) and 10 (Reduced Inequality).

1. Timeframe

22. Field trials for engineered gene drives are likely to be within 5 to 10 years. Releases for vector control could potentially be within 3 to 5 years, while releases for controlling invasive species could be between 5 to 10 years. Species such as rodents, which are less tractable to genetic engineering, could be even longer. The Target Malaria consortium may be nearest to a field testing phase with a living modified *Anopheles gambiae* containing a CRISPR-based engineered gene drive. However, the timeframe could also be longer when considering appropriate risk assessment methodologies, regulations and mechanisms for consent have not yet been full developed or implemented.

23. Far future applications may also include applications to control weed species in agricultural settings, as well as other types of organisms, such as fish, snails, arachnids, fungi and other mammals. Patent filings indicate an increase in applications for controlling agricultural pests.

2. Potential impacts on the objectives of the Convention of Biological Diversity

24. Living modified organisms containing engineered gene drives could have both potential positive and potential negative impacts on the three objectives of the Convention on Biological Diversity. Their impact will likely vary depending on the type of engineered gene drive utilized and anticipated phenotype (e.g., high vs. low threshold, suppression vs. replacement). However, some potential impacts are listed below.

25. Potential positive impacts could include:

- Controlling invasive species to reduce damage to native biodiversity and restore ecosystem functioning (e.g., invasive rodents, overcoming pesticide resistance);
- Reduced disease transmission (e.g., avian malaria in Hawaiian songbirds, prevention of extinctions of susceptible populations);
- Reduced use of chemical pesticides (e.g., reduced adverse impacts of pesticides or poison baits);
- Redcauced human interference and footprint on fragile ecosystems (e.g., physical damage caused by humans on islands); and
- Sharing of benefits over large areas.

26. Potential negative impacts could include:

- Disruption of ecosystems due to removal or suppression of a species from the environment (e.g., induced ecosystem instability, disruption of foodwebs);

- Elimination of an endogenous species if an LMO containing an engineered gene drive spreads to native range of the host organism;
- Elimination or suppression of non-target organisms due to gene flow or hybridization (e.g., *Anopheles sp.* complex);
- Invasion into unintended environments;
- Unintended persistence in the environment due to designed ability to spread;
- Off-target impacts within host organism;
- Reduction in genetic diversity (e.g., reduced fitness, potential increased disease susceptibility, decreased ability of target organism to adapt to environment); and
- Niche replacement (e.g., biological invasion of an alternative disease vector, secondary pest or invasive species).

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

27. Due to the nature of LMOs containing engineered gene drives, several points of consideration may need to be taken into account when considering their risk assessment, risk management and regulation. These could potentially include:

- Spatio-temporal distribution of release (e.g., spread over large distances, long timescales for monitoring and management);
- Treatment of the precautionary principle;
- Lack of appropriate comparators;
- Lack of environmental baseline data;
- Reliability of current models (e.g., inability to accurately simulate whole ecosystem);
- Treatment of uncertainty and emergence of unintended consequences due to ecosystem complexity;
- Stepwise approach to field testing (e.g., complications due to dissemination potential);
- Environmental containment (e.g., islands may not be considered as contained);
- Lack of available risk management measures (e.g., potential irreversibility of release);
- Need for monitoring (e.g., intended and unintended effects);
- Transboundary movements and the need for international cooperation (e.g., dedicated legal instrument for regional cooperation, accidental human-mediated spread due to globalization);
- Effectiveness of current risk assessment methodologies; and
- Lack of comprehensive global governance (e.g., early detection and rapid response mechanisms, lists of species of local concern based on a coordinated risk assessment framework).

4. Limits of knowledge

28. Due to their new development and differing characteristics to commercially available LMOs, such as crops, LMOs containing engineered gene drives could be considered to have higher levels of uncertainty, which may also effect considerations on risk assessment (in subsection 3 above). Potential points of consideration could include:

- Complexity of ecological systems, particular for wild or unmanaged environments (e.g., biotic interactions);
- Population dynamics (e.g., mating behaviour, reproduction rate, genotypic replacement, rebound dynamics);
- Long term stability and evolution of the molecular system (e.g., mutation rate, efficacy of system, resistance);
- Host-pathogen response (e.g., changes in vector competence, evolution of pathogen);
- Incomplete understanding of molecular regulatory mechanisms;
- Environment-by-genome interactions on cells, tissues, organisms and populations;
- Incomplete understanding of polygenic resistance mechanisms in weed-targeting engineered gene drive applications;
- Next-generation effects;
- Unforeseen impacts;
- Potential extrapolation error of experimental data (e.g., lack of empirical data); and
- Effective monitoring strategies.

5. Additional relevant considerations

29. In addition to potential impacts on the objectives of the Convention on Biological Diversity and considerations for risk assessment, management and regulation, there could be potential additional relevant considerations, such as:

- Improved human sustainable development and quality of life through a reduction in disease and economic burden (e.g., improved health, reduced childhood mortality, improved economic security, reduced exposure to chemical pesticides, long term lower cost of intervention);
- Introduction of new pathogens or diseases due to niche-filling;
- Improved food security (e.g., reduced damage from pests, improved livestock health);
- Social, political and commercial determinants of disease (e.g., public health infrastructure, housing, sanitation, education, sustained public health funding);
- Alternative interventions (e.g., in relation to efficacy of the intervention, poverty alleviation, improved sanitation, pesticides, bed nets, traps, Wolbachia-infected mosquitoes, vaccines, transmissible pathogens);
- Cost of inaction;
- Changes to local economies due to reduced presence of an invasive pest or disease vector (e.g., reduced economic losses, improved tourism);
- Concentration of the market to few biotechnological organizations;
- Creation of technology dependence (e.g., ‘technological lock-in’)
- Need for multiple product releases (e.g., controlling multiple vectors or species, combat resistance formation);
- Fairness and disparity between potential positive and potential negative impacts across communities;
- Consent (e.g., large spatial distribution may not allow for individuals to opt out);

- Intellectual property considerations (e.g., access to technology, ownership);
- Indigenous peoples and local communities (e.g., free, prior and informed consent, loss of traditional knowledge, spiritual beliefs);
- Negative changes to traditional methods and communities managing biological resources (e.g., local food production systems, rural communities);
- Ethics (e.g., human intervention in nature, principles of nature conservation, intrinsic value of organisms, protection of pristine nature or culturally important environments);
- Effective public and stakeholder participation (e.g., inclusivity in risk acceptability and decision making, integration of multiple disciplines and cross-cultural knowledge);
- Public outreach and scientific communication (e.g., public consultations, use of local or indigenous languages);
- Transparency in research, development and decision-making (e.g., use of a registry, conflict of interest declarations);
- Field testing in areas outside the jurisdiction of developer;
- Liability and redress;
- Dual-use (e.g., deliberate creation of ecosystem imbalance);
- Need for improved capacity-building and technology transfer;
- Gender considerations (e.g., equal training opportunities for women);
- Intergenerational equity (e.g., considerations of youth and future generations); and
- Conflation of issues (e.g., removal of invasive species from environment vs. technology being deployed).

6. Potential lessons from other domains

30. Several examples in other fields and domains may provide important insights for the consideration of engineered gene drives. Some examples could include:

- The current experience with the use of insecticides and pesticides;
- Experience with other living modified insects that do not contain engineered gene drives (e.g., risk assessment frameworks, self-limiting insects);
- Risk assessments of classic biocontrol and sterile insect technique applications could inform the risk assessment of LMOs containing engineered gene drives;
- Invasive species could provide clues to invasion and spread of an engineered gene drive system;
- Regulation of invasive species (e.g., European Union Regulation 1143/20141 provides for a cross-border 'three-stage hierarchy' of risk management: prevention, early detection, and long-term control);
- Nanotechnology due to its poor retrievability post-release; and
- Existing and ongoing multidisciplinary assessment (e.g., "Intercultural Assessment of Synthetic Biology Applications" follows a participatory assessment approach with indigenous and peasant communities in Chile and Mexico).

[1] Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R1143

31. It is important to note that a process currently underway under the Cartagena Protocol on Biosafety to develop additional voluntary guidance on the risk assessment of LMOs containing engineered gene drives. In addition, relevant resource materials related to detection and identification of LMOs and the Network of Laboratories for the Detection and Identification of Living Modified Organisms are available on the Biosafety Clearing-House[2].

C. Self-limiting insect systems

32. Self-limiting insect systems are applications that are developed to reduce the numbers of disease vector or agricultural insect pests without persisting in the wild populations in the absence of sustained releases. These systems are implemented using transgenic cassettes (e.g., genetic circuits) to improve on sterile insect technique, which involved irradiating males and caused reduced fitness, increased costs and reduced effectiveness. These living modified insects involve releases of modified adult males (first generation) or encapsulated larvae or eggs (second generation), which when the modified adults mate, they do not produce insects that survive to maturity. Research is on-going to develop new systems, such as precision guided sterile insect technique (utilizing CRISPR-Cas), and applications in new insect species. These systems are considered to be "*living modified organisms*" as defined by the Cartagena Protocol on Biosafety.

33. Specific examples of self-limiting insects include the living modified insects developed by Oxitec, such as the living modified *Aedes aegyptii* to control dengue, as well as the living modified diamondback moth (*Plutella xylostella*) and the Friendly™ Fall Armyworm (living modified *Spodoptera frugiperda*) for agricultural settings.

1. Timeframe

34. Field trials for self-limiting insects have occurred in United States (mosquitoes and diamondback moth), Brazil (mosquitoes and fall armyworm), Cayman Islands (mosquitoes), China (mosquitoes) and Burkina Faso (male-biased *Anopheles gambiae* mosquitoes). Other field trials are ongoing (e.g., in the case of Oxitec's second generation living modified *Aedes aegyptii*). Several other species are under development. Regarding other self-limiting systems, such as those based on the precision guided sterile insect technique, field trials could be within 10 years (e.g., living modified *Anopheles gambiae* in The Gambia). However, timeframes may vary depending on the developmental stage of the application and regulatory approval.

2. Potential impacts on the objectives of the Convention of Biological Diversity

35. Self-limiting insect systems are likely to have impacts similar to other living modified insects aimed at reducing disease burden or controlling insect pests on the three objectives of the Convention on Biological Diversity. These potential impacts could be positive or negative and are listed below.

36. Potential positive impacts may include:

- Reduced disease burden and transmission of vector-borne diseases;
- Control agricultural pests;
- Reduced chemical pesticide use (e.g., reduced adverse impacts of broad-spectrum pesticides); and
- Control of invasive insect species.

37. However, there could also be potential negatives impacts, which could include:

- Population collapses (e.g., disruption to food webs)

[2] The Network of Laboratories for the Detection and Identification of Living Modified Organisms is available at: https://bch.cbd.int/en/portals/detection/network-of-labs. Biosafety Technical Series 05: Training Manual on the Detection and Identification of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety is available at: https://bch.cbd.int/en/database/VLR/BCH-VLR-SCBD-260177-3

- Population dynamics (e.g., population rebounds following release)
- Niche replacement (e.g., biological invasion of an alternative disease vector, secondary pest or invasive species);
- Horizontal gene transfer (e.g., causing unintended effects in non-target populations);
- Unintended releases or persistence (e.g., unexpected survival of lethality cassettes);
- Hybridization due to the use of non-native strains for transformations;
- Use of antibiotics to rear living modified insects; and
- Introduction of novel toxins or induction of allergenicity.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

38. Due to the self-limiting nature of the modified insects, the risk assessment process could potentially be simpler compared to other modified insect applications, which could persist in the environment for longer durations. Despite this, the following points may necessitate further consideration:

- Genetic stability and incomplete phenotypic expression of selective lethality;
- Next-generation effects;
- Large spatial distribution (e.g., transboundary movements, buffer zones);
- Availability of data on potential impacts on native species;
- Treatment of uncertainties; and
- Need for monitoring for intended and unintended effects.

39. Regarding the availability of tools for detection and identification, genetic methods based on protein or DNA techniques have not yet been developed for field use. Currently, monitoring is conducted using traps and fluorescent protein markers for visual detection. Thus, further development of detection and identification methodologies might be required.

4. Limits of knowledge

40. In terms of potential limitations to current knowledge about self-limiting insect systems, some considerations may include:

- Availability of environmental baseline data (e.g., population densities, biotic interactions, spatial distribution and movement);
- Impacts of horizontal gene transfer;
- Availability of data demonstrating efficacy of the intervention and supressing disease; and
- Lower amount of data generated on newer self-limiting insect systems (e.g., precision guided sterile insect technique).

5. Additional relevant impacts

41. In addition to the potential impacts of the use of self-limiting insect systems on the Convention on Biological Diversity, there could also be additional relevant considerations to take into account. These may potentially include:

- Human health (e.g., reduction of deaths caused by vector-borne diseases such as malaria and dengue and yellow fever, reduced chemical pesticide exposure, novel allergenicity or toxicity due to ingestion or exposure);

- Economic (e.g., reduced health care costs, decreased loss of economic output related to illness and death, increased economic security in affected communities, reduced agricultural losses);
- Economic sustainability (e.g., high cost if efficacy is low, potential need for multiple releases, reliance on the use of additional products in conjunction);
- Considerations of alternative interventions;
- Access to information (e.g., data generated for assessments, limitations not published)
- Loss of traditional knowledge (e.g., reliance on technological solutions);
- Free, prior and informed consent of indigenous peoples and local communities;
- Individual consent (e.g., large distribution may not enable individuals to opt-out);
- Fairness and disparity between potential positive and potential negative impacts (e.g., select individuals may benefit from positive impacts while whole community may be affected by potential negative impacts, incompatibility with small-holder farming systems to allow for potential benefits);
- Liability and redress;
- Political considerations (e.g., global public health agendas);
- Public and stakeholder engagement in decision-making; and
- Clear scientific communication.

6. Potential lessons from other domains

42. For self-limiting insect systems, there is a growing body of scientific and peer-reviewed literature available for systems based on genetic circuits (e.g., those that aim to replace sterile insect technique). However, lessons could also be learned from conventional sterile insect technique, incompatible insect technique and other forms of biocontrol. Additionally, data and information collected during evaluations of these systems could be useful for the risk assessment of other modified insects, such as those containing engineered gene drives.

D. Integration of artificial intelligence and machine learning

43. Advances in machine learning and artificial intelligence have led to an increase in their utilization for the development of synthetic biology applications. These algorithms use mathematical models (e.g., neural networks) and large datasets (e.g., chemical information, sequencing data) to inform the engineering or creation of synthetic biology organisms, products and parts. In addition, programmes have also been utilized to predict outcomes of genetic interventions, support experimental design and facilitate automated searches of large databases.

44. Artificial intelligence and machine learning are enabling the re-engineering, re-imagining and creation of a diverse range of applications including enzymes, catalysts, food ingredients, pharmaceuticals, biomaterials, coatings, gene therapies and chemical production, among others. Some specific examples include:

- Machine learning-aided protein engineering (e.g., hydrolases for polyethylene terephthalate depolymerization, plant metabolite production in synthetic microbial applications, novel functional lysozymes, enzymes to transform bitter compounds in stevia to sweeter variants (Arzeda));
- Protein folding predictions to streamline biosynthesis across various industries (e.g., Alpha Fold and ESMFold);

- Machine learning models for the creation of novel, customized proteins (e.g., ProtGPT2, Chroma, ProGEN);
- Text-to-DNA and text-to-protein applications (e.g., translating text or language prompts into genetic elements or polypeptides, such as DNA-Diffusion, ProteinDT);
- Automated closed-loop laboratories facilitated by artificial intelligence;
- Bio-computation to overcome the limitations in silicon-based computation (e.g., leveraging the computing capacity of engineered organisms like Escherichia coli, DNA data storage, biological processing units based on in vitro neural cell cultures (Cortical Labs)); and
- Responsive crops and artificial intelligence-guided precision agriculture (e.g., InnerPlant developed engineered plants to emit fluorescent signals when stressed, which can be monitored by satellites and John Deere agricultural equipment cameras).

45. Due to the transformative nature of these tools, artificial intelligence-designed applications of synthetic biology may impact both the Kunming-Montreal Global Diversity Framework Targets and United Nations Sustainable Development Goals. For example, artificial intelligence-guided metabolic engineering potentially contribute to the United Nations Sustainable Development Goals, particularly 1 (No Poverty), 2 (Zero Hunger), 3 (Good Health and Well-Being), 6 (Clean Water and Sanitation), 7 (Affordable and Clean Energy), 12 (Responsible Consumption and Production), 13 (Climate Action), 14 (Life Below Water) and 15 (Life on Land).

1. Timeframe

46. Applications of synthetic biology designed and developed using artificial intelligence tools are already in use. However, significant investments in research are anticipated within the next 5 years. Several artificial intelligence and computing companies (e.g., Meta, Google/Deep Mind, Microsoft, NVIDIA, Salesforce and Stability AI) are entering into agreements or joint ventures with biotechnological companies (e.g., Gingko Bioworks) and/or institutes (e.g., Broad Institute). Given rapid development and use of artificial intelligence in other industries, impacts could be immediate or near-term. Further, based on the experience with large language models, such as the ChatGPT and Dall-E applications, generative artificial intelligence could soon also be taken up in the field of synthetic biology (e.g., genomic-scale language models, protein language models).

2. Potential impacts on the objectives of the Convention of Biological Diversity

47. Regarding the convergence of artificial intelligence and machine learning with synthetic biology, there could be impacts on the three objectives of the Convention on Biological Diversity depending on the application in use.

48. Some potential positive impacts could include:

- Aiding in conservation efforts, such as predicting and preventing zoonotic disease outbreaks;
- Reduced reliance on non-sustainable uses of biological diversity;
- Climate change mitigation (e.g., facilitate creation of biosequestration systems, replacement of fossil fuels); and
- Supporting ecosystem diversity and health (e.g., applications to degrade of plastics and environmental pollution, improved freshwater use efficiency through the use of halotrophic organisms).

49. Some potential negative impacts could include:

- Harm to biological diversity through accidental releases or misuse of technology;
- Disruption of the sustainable use of biological diversity, particularly in Global South (e.g., flavours, fragrances and cosmetics);

- Negative changes in land and ocean use; and
- Facilitated use of genetic resources without benefits-sharing (e.g., biopiracy, lack of informed consent or material transfer agreements).

3. Potential gaps to risk assessment, risk management and regulation and availability of tools for detection, identification and monitoring

50. The use of artificial intelligence in synthetic biology could raise pertinent considerations for risk assessment, risk management and regulation of these types of synthetic biology applications, including its relationship to the precautionary principle. Some potential points to consider could be:

- Challenges to assessment (e.g., novel synthetic pathways and genetic circuits, complex biological activity of proteins on molecular processes);
- Extensive use of biological data by artificial intelligence systems complicates the governance and fair sharing of benefits from digital sequence information (e.g., attribution to source(s), traceability);
- Use of digital sequence information without consent could challenge provisions in the Convention on Biological Diversity and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (e.g., in design or as part of training datasets);
- Text-to-DNA and text-to-protein applications lower barriers for amateurs and small players, posing challenges in detection, monitoring, governance and containment;
- Need for global cooperation and benefits-sharing;
- Gap in international environmental regulation for synthetic de novo proteins;
- Decentralized production and regulation;
- Increased scale of certainties and uncertainties; and
- Need for monitoring and reporting mechanism for artificial intelligence-designed organisms.

4. Limits of knowledge

51. Due to the transformational nature of the artificial intelligence and recent application to the field of synthetic biology, some potential limits in knowledge could exist and may include:

- Unknown biosafety risks due to the complexity and unpredictability of ecosystem interactions with novel applications (e.g., synthetic proteins, novel genetic sequences);
- Persistence of synthetic proteins in environment;
- Availability of reliable forecasting for impacts on ecosystems (e.g., the availability of genomic, transcriptomic and proteomic data to predict potential effects, understanding of the multitude of protein interactions at a cellular level);
- Precision and accuracy of artificial intelligence and machine-learning models (e.g., outputs are probability based, impacts of biases in training datasets);
- Ability to explain results of an artificial intelligence model (e.g., erroneous outputs); and
- Lack of experience with the creation of novel organisms and novel emerging applications (e.g., bio-computing).

5. Additional relevant impacts

52. Beyond the impacts on the objectives of the Convention, the use of artificial intelligence and machine learning for the creation of applications of synthetic biology, may pose additional relevant considerations. These could potentially include:

- Accelerated development of synthetic biology applications;
- Increased efficiency and optimization of bioproduction;
- Informed vaccine design (e.g., pandemic prevention);
- Market concentration in a few companies;
- Required reliance on additional commercial products (e.g., 'technological lock-in');
- Shifts in industries and supply chains (e.g., economic losses for small-scale farmers, natural product producers, economies reliant on biological diversity);
- Lower barrier for the creation of modified organism in low containment or without regulatory oversight;
- Biosecurity implications, including dual or military use of applications (e.g., creation of toxins or harmful compounds, misuse of text-to-protein models);
- Susceptibility of training datasets to poisoning;
- Lack of transparency in the decision making of artificial intelligence models;
- Availability and quality of datasets (e.g., overrepresentation of crop varieties grown in Global North or optimized for commercial use);
- Liability and redress;
- Intellectual property and ownership considerations; and
- Equity and consent (e.g., use of traditional knowledge, control of genetic resources).

6. Potential lessons from other domains

53. When considering the use of artificial intelligence and machine learning in synthetic biology, some important lessons could be taken from the utilization of artificial intelligence in other sectors, including the management of bias in training data and ethics in artificial intelligence. Recently, the European Union passed regulations to ensure "explainable artificial intelligence" to improve transparency in artificial intelligence systems.

54. Further, historical examples of the early synthetic chemical industry and unintended environmental impacts could also potentially inform the treatment and management of the environmental use of synthetic proteins. In addition, current experience with LMOs could also inform potential risk assessment, risk management and regulation of organisms designed by artificial intelligence.

E. Inequity in the participation of developing countries in the context of synthetic biology

55. Developed countries represent the leaders in the research and development within the field of synthetic biology. However, the participation of developing countries in both the research and development in synthetic biology could be important for achieving the objectives of the Convention on Biological Diversity, particularly for the equitable sharing of the benefits arising out of the utilization of genetic resources. Despite this, developing countries currently face challenges in their ability to research, access and use the technology, thus resulting in inequitable participation. Currently, Latin America, the Middle East and Africa contribute an estimated 7% of the total market value of synthetic biology.

56. The level of participation in the research and development of synthetic biology could have an influence on Targets 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) and 20 (Strengthen Capacity-Building, Technology Transfer, and Scientific and Technical Cooperation for Biodiversity) of the Kunming-Montreal Global Biodiversity Framework.

1. Timeframe

57. The issue of inequity in the field of synthetic biology is considered to be current and ongoing.

2. Potential impacts on the objectives of the Convention of Biological Diversity

58. When considering equitable participation of developing countries in the field of synthetic biology, the following potential positive impacts could be enabled:

- Improved implementation of Articles 16, 17, 18 and 19 of the Convention on Biological Diversity;
- Preservation of ecosystems and habitat restoration;
- Sustainable agriculture practices (e.g., improved soil fertility, improved climate resilience, reduced impact of conventional or traditional farming practices);
- Reduced pressures on biological diversity due to pollution, pesticides and waste;
- Improved land use;
- Enable monitoring of biological diversity;
- Improved sustainable use of biological diversity;
- Fair and equitable benefits sharing; and
- Cataloguing of genetic resources (e.g., understanding national genetic biodiversity, improved benefits sharing).

59. When considering inequitable participation of developing countries in the field of synthetic biology, potential negative impacts could include:

- Hindered ability to access the potential benefits of synthetic biology applications; and
- Developing countries could remain primarily as exporters of raw materials, which could cause a reliance on resource extraction and negatively impact conservation efforts.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

60. Regarding risk assessment, risk management and regulation of synthetic biology, specific considerations for developing countries may include:

- Limited access to technology and resources may hinder the ability to conduct thorough risk assessments;
- Need for capacity-building and further awareness of the applications of synthetic biology (e.g., experience assessing applications of synthetic biology has implications on the effectiveness of risk assessment and regulation);
- Improved bureaucracy to prevent research delays (e.g., contracts for access to genetic resources);
- Appropriate regulatory frameworks (e.g., alignment to specific needs and context, prevention of adverse impacts);
- Need for ethical guidelines for the development of synthetic biology;

- Need for government prioritization and enabling policies;
- Increased resource mobilization; and
- Need for global collaboration and cooperation.

61. The tools for detection, identification and monitoring of the applications of synthetic biology are available to some extent in developing countries. However, multiple entry ports-of-entry, increased volumes due to growing economies, lack of laboratory infrastructure, training personnel and available resources impact their effective use. In addition, access to next-generation sequencing technologies is needed for nations to derive fair and equitable benefits from their genetic resources.

4. Limits of knowledge

62. Limited information is available regarding potential limits of knowledge in relation to the inequity in the participation of developing countries in the context of synthetic biology. However, in general, questions remain regarding current levels of knowledge on how changes induced by synthetic biology interventions impact the functioning of biological systems and interactions within ecosystems.

5. Additional relevant impacts

63. The inequity in the participation of developing countries in the context of synthetic biology raises several additional relevant impacts beyond impacts on the objectives of the Convention of Biological Diversity and regulatory considerations. Some of these considerations are detailed below.

64. Equitable participation of developing countries could potentially result in:

- Improved health (e.g., enhanced nutrition of crops, vaccine development, novel diagnostic tools for healthcare);
- Improved food security;
- Poverty alleviation;
- Creation of sustainable bio-economies and shift from petroleum-based economic activities;
- Inclusion in the global growth of the synthetic biology market;
- Creation of additional socioeconomic value from resources; and
- Fostering local innovation (e.g., adapting orphan crops to new biotic or abiotic stressors, support for research jobs in developing countries, novel nature-inspired applications).

65. Inequitable participation of developing countries could potentially result in:

- Continued dominance by Global North in the research and development of synthetic biology;
- Dependence on developed nations for access to technology (e.g., widening economic gap between developed and developing nations);
- Poor participation in discussions and debates on the applications of synthetic biology; and
- Underutilized research potential of developing countries.

6. Potential lessons from other domains

66. To further promote the equitable participation of developing countries in synthetic biology, lessons from promoting inclusivity in scientific research and similar technology transfer initiatives should be explored. In addition, experience with current LMOs could provide a foundation for understanding and assessing the applications of synthetic biology on a case-by-case basis and in accordance with national circumstances. In addition, lessons could also be learned by following a stepwise approach during research and development of synthetic biology applications to allow for a continual collection and assessment of information. Furthermore, experience with research,

capacity-building and technology transfer initiatives could facilitate fair and equitable benefits-sharing.

III. Additional trends and issues in synthetic biology prioritized by the multidisciplinary Expert Group

A. Use of synthetic biology in wild organisms in the context of resilience in threatened species

67. The use of synthetic biology in wild organisms in the context of resilience in threatened species aims to assist conservation efforts for endangered or threatened species by introducing or reinforcing genetic diversity and conferring resilience to biotic and/or abiotic pressures. Approaches could entail engineering protected species, precision conversation strategies and assisted evolution.

68. Some specific examples of applications could include:

- Engineered American chestnut trees for blight resistance;
- In vivo germ-line genome editing directly into wild bird populations for disease resistance (e.g., malaria resistance in Hawaiian honeycreepers);
- Inheritable immunity to sylvatic plague in critically endangered black-footed ferrets;
- Enhanced thermal tolerance in coral and kelp species;
- Engineered chytrid resistance in frogs;
- Cane toad toxin resistance in Northern Quolls, Australia; and
- Modification of honeybee microbiome for greater pest resilience.

69. Synthetic biology approaches to improve resilience in threatened species might be relevant for the goals and targets of the Kunming-Montreal Global Biodiversity Framework, such as Targets 9 (Manage Wild Species Sustainably To Benefit People), 10 (Enhance Biodiversity and Sustainability in Agriculture, Aquaculture, Fisheries, and Forestry) and 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology). Particularly, for Target 17, further strengthening of biosafety measures might be required to account for gaps in risk assessment and risk management.

1. Timeframe

70. The timeframe varies for these applications. Some applications are near-term, such as the blight-resistant American chestnut (under regulatory review for release) and other are far-future and still in experimental stages, such as chytridiomycosis-resistant frogs (over 10 years away from release).

2. Potential impacts on the objectives of the Convention of Biological Diversity

71. The use of synthetic biology in wild organisms in the context of resilience in threatened species could have both positive and negative impacts particularly on the first objective of the Convention on Biological Diversity.

72. Some potential positive impacts on the conversation of biological diversity include:

- Tolerance to abiotic stress (e.g., thermal stress, climate change);
- Resistance to biotic stress (e.g., pathogens, pests);
- Increased or maintenance of current genetic diversity;
- Restoration of lost genetic diversity;
- Reduction in insect vector disease transmission; and

- Reverse decline of and increase the number of critically endangered species.

73. Some potential negative impacts on the conversation of biological diversity include:

- Unintended impacts on native flora, fauna and microbes;
- Changes to ecosystem dynamics, such as the biotic-biotic and biotic-abiotic interactions, leading to biodiversity loss;
- Increased competitiveness (e.g., outcompete native species);
- Increased invasiveness;
- Unintended impacts of genetic modification and off-target genome editing (e.g., increased susceptibility to other diseases, invasiveness, loss of genetic diversity, development of toxins, changed cellular regulation); and
- Gene flow (e.g., transfer of antibiotic or herbicide resistance gene cassettes into wild relatives).

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

74. When considering the use of synthetic biology in wild organisms in the context of resilience in threatened species, the Cartagena Protocol on Biosafety is an important instrument support the process of risk assessment of these applications. However, potential challenges to risk assessment, risk management and regulation may still exist. These could include:

- Use of synthetic biology in unmanaged or wild environments;
- Accounting for complexity of ecosystems (e.g., from molecular to ecosystem level);
- Co-existence of modified and non-modified organisms;
- Lack of risk management measures (e.g., irreversibility of release, large spatio-temporal distribution);
- Limited availability of data on whole ecosystems (e.g., species relationships);
- Extrapolation of laboratory or contained use data (e.g., predicting environmental impacts); and
- Transboundary movements.

4. Limits of knowledge

75. In terms of potential limitations to current knowledge about the use of synthetic biology in wild organisms in the context of resilience in threatened species, some considerations may include:

- Behaviour of organisms in the environment;
- Complex biotic relationships in ecosystems (e.g., forest microbiomes, mycorrhizal interactions and mutualistic communities); and
- Invasion biology.

5. Additional relevant considerations

76. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, and potential challenges to risk assessment, risk management and regulation, the use of synthetic biology in wild organisms in the context of resilience in threatened species could also raise additional relevant considerations. Some potential points may include:

- Facilitation of responsible innovation and sustainable development;
- Access to technology in developing countries;

- Liability and redress;
- Ethics (e.g., concept of nature and natural, value of nature, human intervention in nature);
- Free prior and informed consent of indigenous peoples and local communities;
- Attitudes of the public and indigenous peoples and local communities towards engineered species for conservation could be dynamic and change;
- Importance of stakeholder engagement;
- Loss of benefits to provider countries (e.g., when endemic species are found or engineered elsewhere); and
- Diversion from other conservation measures and approaches.

B. Synthetic biology applications for bioremediation, biodegradation or biomining

77. Synthetic biology applications for bioremediation, biodegradation or biomining aim to assist with waste management of environmental pollution, recycling of resources or recovery of valuable metals from the environment. These applications are engineered to degrade, sequester or transform environmental pollutants, as well as precipitate or extract valuable metals using metabolic and/or protein engineering. Specific examples include:

- Engineered applications to detect and sequester pollutants, such as arsenic (e.g., biosensing engineered bacteria to signal presence of specific pollutants);
- Biosensors for detecting aromatic hydrocarbons (e.g., transcription factor coupled to fluorescent protein expression system based on gene circuits)
- Hexachlorobenzene degrading bacteria using a cytochrome P-450cam variant;
- Modifying microbes for plastic recycling (e.g., nylon, polyurethane and polyethylene terephthalate);
- Biosynthesis of a granular material that attracts and sticks to micropollutants such as pesticides, pharmaceuticals and certain chemicals in wastewater;
- Multicellular structured “synthetic jellyfish” to degrade contaminants after an oil spill;
- Novel approaches to detecting, removing and recycling perfluoroalkyl and polyfluoroalkyl substances from water (e.g., engineering proteins to precisely bind per- and polyfluoroalkyl substances);
- Microbial products that sequester radioactive elements through biosorption and biomineralization processes and/or through direct and indirect redox transformation; and
- Designing microbes for sustainable and more efficient extraction of energy transition metals (e.g., copper and lithium).

78. Synthetic biology application for bioremediation, biodegradation or biomining could be relevant for Kunming-Montreal Global Biodiversity Targets 9 (Manage Wild Species Sustainably To Benefit People), 10 (Enhance Biodiversity and Sustainability in Agriculture, Aquaculture, Fisheries, and Forestry) and 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology). Further, these applications may also be relevant for several United Nations Sustainable Development Goals, such as 2 (Zero Hunger), 6 (Clean Water and Sanitation), 7 (Affordable and Clean Energy), 9 (Industry, Innovation and Infrastructure), 11 (Sustainable Cities and Communities), 12 (Responsible Consumption and Production), 13 (Climate Action), 14 (Life Below Water) and 15 (Life on Land).

1. Timeframe

79. Many applications are in various stages of research, development and release with many being near or medium term. For example, introduction of modified bacteria and enzymes into bioreactors, oceans and landfills is expected in the next 3 to 5 years, pending regulatory review while application for the remediation of per-and polyfluoroalkyl substances could be in 5 to 0 years. Further, several research groups are tackling the challenge of accelerating microbial digestion of multiple plastic-based pollutants.

2. Potential impacts on the objectives of the Convention of Biological Diversity

80. Synthetic biology applications for bioremediation, biodegradation or biomining could have both positive and negative impacts on the objectives of the Convention on Biological Diversity, particularly for the conservation and sustainable use of biological diversity.

81. Some potential positive impacts may include:

- Conservation of natural resources and biodiversity;
- Reduction and removal environmental pollution (e.g., heavy metals, pesticides, pharmaceuticals);
- Remediation of contaminated environments (e.g., from oil spills); and
- Reduced use of toxic compounds.

82. Some potential negative impacts may include:

- Outcompeting native soil microorganisms (e.g., extinctions, loss of diversity);
- Adverse effects on soil function and soil ecosystems (e.g., disrupting or disturbing biotic interactions);
- Gene transfer (e.g., unintended prolonged effects or novel phenotypes in the environment);
- Land use changes (e.g., extraction activities on ecologically significant areas); and
- Unintended adverse effects.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

83. When considering the synthetic biology applications for bioremediation, biodegradation or biomining, the Cartagena Protocol on Biosafety is an important instrument support the process of risk assessment of these applications. Despite this, potential challenges to risk assessment, risk management and regulation may exist, including sufficiency of available data (e.g., environmental interactions) and treatment of the precautionary principle (e.g., cut-off criteria). However, risk could also be mitigated through the use of microbes with high environmental specificity and further data could be gathered using controlled experiments.

4. Additional relevant considerations

84. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, the development of synthetic biology applications for bioremediation, biodegradation or biomining should include a careful consideration of the social, ethical, and biosafety dimensions of the research, alongside the intellectual merit, potential profitability or broader positive impacts.

85. Further potential considerations may also include:

- Enhanced quality of life for communities affected by environmental pollution (e.g., improved health outcomes);

- Alternatives to environmental emergency response (e.g., locally adapted solutions for oil spills);
- Shift in focus away from preventing the initial environmental pollution; and
- Increase extraction activities on culturally significant areas.

C. Microbiome engineering for non-medical purposes

86. Microbiome engineering for non-medical purposes focuses on the modification of microbiomes associated with plants, fungi, animals, soils, water, among other organisms and environments. These approaches may also relate to the assembly of synthetic microbial communities with optimized genotypes and phenotypes to address environmental or agricultural concerns. The modification process may involve transgenic and/or genome editing techniques.

87. Some specific examples of applications that could be considered as part of this item include:

- Engineered symbiotic nitrogen-fixing microbes that associate with the roots of crop plants (e.g., maize, wheat, rice);
- Engineered microbiome to protect crops from frost damage;
- Engineered microbes that assist plants to resist pests and diseases;
- Modified soil microbiomes for carbon sequestration (e.g., Audacious project);
- Engineering insect microbiomes for paratransgenetic applications;
- Antibody treatments for modulating livestock microbiome for reduced methane emissions;
- Engineered microbes that reduce methane production from ruminant livestock;
- Varroa mite-resistant honeybees by modifying gut microbiome;
- Increased thermal tolerance in corals;
- Increased chytridiomycosis resistance in frogs;
- Modification of animal microbiomes through selective targeting of bacterial species (e.g., phage-mediated delivery of CRIPSR to kill specific species and bacterial genome editing (Guided Biotics by Folium Science)); and
- Microbial consortia for bioproduction (e.g., petrochemical equivalents, industrial chemicals, materials).

88. The microbiome engineering could have impacts on Targets 10 (Enhance Biodiversity and Sustainability in Agriculture, Aquaculture, Fisheries, and Forestry) and Target 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) of the Kunming-Montreal Global Biodiversity Framework. In addition, these applications may also contribute directly to the Sustainable Development Goals 7 (Affordable and Clean Energy), 9 (Industry, Innovation and Infrastructure), 12 (Responsible Consumption and Production), 13 (Climate Action) and 15 (Life on Land).

1. Timeframe

89. Applications are under various stages of research, development and commercialization. The majority of research is currently focused on the modification of one or two species in a microbiome. Near-term examples include microbial treatments to replace nitrogen fertilizers (commercialized), Guided Biotics (under regulatory approval) and anti-Varroa mite microbes (field trials).

2. Potential impacts on the objectives of the Convention of Biological Diversity

90. Microbiome engineering for non-medical purposes could have both positive and negative impacts on the objectives of the Convention on Biological Diversity, particularly for conservation and sustainable use of biological diversity.

91. Some potential positive impacts could include:

- Pest and disease resistance;
- Tolerance to abiotic stress (e.g., thermal stress, climate change);
- Reduced use of antibiotic (e.g., lowered risk of antibiotic resistance);
- Reduced dependence on chemical fertilizers;
- Reduced methane emissions from ruminants; and
- Carbon-negative chemical manufacturing (e.g., reduction of greenhouse gases).

92. Some potential negative impacts could include:

- Disruption of natural or agroecological microbiome function;
- Perturbation of ecosystem functions (e.g., disruption of symbiotic relationships);
- Horizontal gene transfer resulting in the spread of antibiotic resistance genes or genetic cassettes (e.g., unintended phenotypes, phenotypic persistence);
- Risk for the development of pathogenicity; and
- Unintended, off-target and unforeseen impacts.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

93. When considering microbiome engineering for non-medical purposes, the Cartagena Protocol on Biosafety is an important instrument support the process of risk assessment of these applications. Despite this, potential challenges to risk assessment, risk management and regulation may still exist. These could potentially include:

- Modification of organisms in their native environments (e.g., modification outside biosafety regulations);
- Containment challenges (e.g., interconnectedness of microbiomes, accidental escape);
- Potential for spread and transboundary movements; and
- Regulatory status if genome-edited (e.g., mixed regulation for genome edited products).

4. Limits of knowledge

94. Despite a recent and growing body of literature on microbiomes for medical purposes, a high degree of uncertainty may be related to non-medical microbiome engineering due to a lack of knowledge to non-human microbiomes. Thus, some potential points for further consideration may include:

- Limited knowledge on microbiomes in general;
- Complexity of partnership networks;
- Microbial and pathogen evolution;
- Indirect effects of microbiomes on soil and plant health; and
- Cumulative effects.

5. Additional relevant considerations

95. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, and potential challenges to risk assessment, risk management and regulation, microbiome engineering for non-medical purposes could also raise additional relevant considerations. Some potential points may include:

- Human health (e.g., reduced antibiotic resistance in food-borne pathogens, reduced exposure to agricultural chemicals, accidental consumption);
- Human microbiomes (e.g., horizontal gene transfer, accidental consumption);
- Organic farming (e.g., spread of modified microorganisms onto organic farms);
- Creation of new low-carbon or circular economies in the case of biomanufacturing applications;
- Intellectual property (e.g., patenting of microbes could impact farmers and stakeholders involved in agri-food system);
- Free, prior and informed consent of indigenous peoples and local communities (e.g., spread onto traditional lands and waters); and
- Public engagement.

D. Engineered bacteria for nitrogen-fixation and fertilizers

96. Applications of engineered bacteria for nitrogen-fixation and fertilizers aim to use microbial engineering to replace chemical inputs into agricultural systems, such as fertilizers. In the case of nitrogen, these applications aspire to the replace ammonia fertilizers, produced through the Haber-Bosch process. One specific example could be engineered bacteria developed by PivotBio, which colonizes maize roots and fixes nitrogen for the plants.

97. Engineered bacteria for nitrogen-fixation and fertilizers may have considerations for Target 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) of the Kunming-Montreal Global Biodiversity Framework, the Soil Conservation Strategy by the Food and Agriculture Organization of the United Nations and the Secretariat of the Convention on Biological Diversity and United Nations Sustainable Development Goal 2 (Zero Hunger).

1. Timeframe

98. The engineered bacteria developed by PivotBio are commercially available in North America. Other engineered (single) microbes with greater capacity to fix nitrogen for maize, barley and wheat systems could be commercialized in the near-term, while consortia might only be available in 10 years or longer.

2. Potential impacts on the objectives of the Convention of Biological Diversity

99. The use of engineered bacteria for nitrogen-fixation and fertilizers could have both positive and negative impacts on the objectives of the Convention on Biological Diversity, particularly for sustainable use of biological diversity.

100. Some potential positive impacts may include:

- Energy efficiency for the production of ammonia fertilizers (e.g., reduced emissions depending on energy infrastructure);
- Reduction of environmental pollution from agricultural run-off that leads to declines in fish and other aquatic organisms (e.g., through eutrophication);
- Reduced chemical inputs into agricultural systems (e.g., reduced environmental impact due to agriculture, efficient resource use); and

- Reduction in greenhouse gases (e.g., assist with emissions reductions).

101. Some potential negative impacts may include:

- Increased invasiveness;
- Increased fitness (e.g., displacement of beneficially microorganisms);
- Unintended impacts on due to altered metabolic functions; and
- Negative impacts on animal microbiomes due to exposure.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

102. When considering risk assessment and risk management of engineered bacteria for nitrogen-fixation and fertilizers, natural (non-modified) biological fixation is likely to provide an appropriate comparator to inform the process of risk assessment. However, following may complicate or pose challenges to the risk assessment of such organisms:

- Containment (e.g., lack of ability to retrieve organisms once released);
- Potential for transboundary movements; and
- Persistence (e.g., phenotypic persistence due to horizontal gene transfer to other species; colonization).

4. Additional relevant considerations

103. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, and potential challenges to risk assessment, risk management and regulation, engineered bacteria for nitrogen-fixation and fertilizers could also raise additional relevant considerations, such as:

- Cost savings for producer (e.g., reduced procurement of fertilizers);
- Increased soil fertility and productivity;
- Intellectual property (e.g., relationship between patents and food systems); and
- Access to information and lack of transparency.

E. Genome-edited plants

104. When referring to genome edited plants, applications are based on the precise genetic modification of a plant species to induce a variety of different traits, such as herbicide tolerance, pest resistance or improved composition, among many others. Tools, such as CRISPR,[3] induce genetic modifications that range from having single nucleotide variations (e.g., additions, deletions, conversions) to precise additions of genetic sequences (e.g., integration of a gene cassette into a define location on a chromosome, genetic sequence replacements) to complex rearrangements of genetic material. Other applications may also have a series of genomic edits in one plant variety, such as de novo domestication of wild crop relatives.

105. In general, research and development are largely focused on agricultural crop species, but genome editing may also be applied to ornamental flowers and trees. Some specific examples of genome-edited plants include:

- Soybean with high-oleic acid levels;
- Disease resistant banana, cassava, maize, potato and rice;

[3] Other tools, such as meganucleases, zinc finger nucleases and oligonucleotide-directed mutagenesis can also be used to produce single or few base pair changes in plant systems.

- Cyanide-free cassava;
- Low-arsenic rice;
- Mustard greens with reduced bitterness; and
- Reduced methane emitting rice.

106. Genome edited plants may have contributions to Target 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) of the Kunming-Montreal Global Biodiversity Framework through research on detection and identification and risk assessment to strengthen biosafety capacity. Other targets that could be impacted may include Targets 2 (Restore 30% of All Degraded Ecosystems), 7 (Reduce Pollution to Levels That Are Not Harmful to Biodiversity), Target 9 (Manage Wild Species Sustainably To Benefit People), 10 (Enhance Biodiversity and Sustainability in Agriculture, Aquaculture, Fisheries, and Forestry), 14 (Integrate Biodiversity in Decision-Making at Every Level) and 15 (Businesses Assess, Disclose and Reduce Biodiversity-Related Risks and Negative Impacts). However, it is important to recognize that genome edited plants may have the potential to both assist and hinder the achievement of these targets, depending on the specific traits and manner in which they are used.

107. Further, these applications may also support several United Nations Sustainable Development Goals, such as 1 (No Poverty), 2 (Zero Hunger), 3 (Good Health and Well-Being), 9 (Industry, Innovation and Infrastructure), 12 (Responsible Consumption and Production), 13 (Climate Action) and 15 (Life on Land).

1. Timeframe

108. Genome edited plants containing small mutations, such as single nucleotide variations or knockouts, have already been authorized, including a high-amylopectin waxy corn and *Camelina sativa* with enhanced omega-3 oil in the United States, as well as a tomato with increased γ-aminobutyric acid levels in Japan and a high oleic soybean in China. Further increases can be expected in the near-term. For plants containing complex genetic rearrangements, commercialization may take over 10 years as further research is required.

109. In addition, it would be important to note that for commercial use, genome-edited varieties would still require several years of breeding and selection before integration into commercial varieties despite the potential speed in development in comparison to other genetic engineering technologies, such as those based on transgenesis.

2. Potential impacts on the objectives of the Convention of Biological Diversity

110. Genome-edited plants may have both positive and negative impacts on the objectives of the Convention on Biological Diversity, but these will depend on the specific characteristics of the plant.

111. Some potential positive impacts include:

- Tolerance to abiotic stress (e.g., drought, climatic adaptation);
- Resistance to pests and pathogens (e.g., reduced use of plant protection products);
- Enhanced carbon storage in root systems;
- Improved nutritional content;
- Improved photosynthesis;
- Increased yield;
- Improved soil quality (e.g., protecting soil biodiversity, reduced soil erosion);
- Improved resource and land use efficiency; and

- Enable sustainable use of biological diversity (e.g., enabling product of natural plant metabolites in non-endangered species).

112. Some potential negative impacts may include:

- Increased use of pesticides or herbicides (e.g., traits that enable chemical product use);
- Changes to structure or nutritional content (e.g., unsuitable for consumption by wild animals);
- Hybridization with native plant species (e.g., reduced genetic diversity);
- Changes to toxicity and allergenicity of the plant;
- Unintended on-target and off-target effects (e.g., mutations, complex rearrangements, translocations, insertions and deletions, foreign DNA incorporation);
- Altered cellular regulation (e.g., production of aberrant peptides, changes in metabolite levels);
- Intensification of agricultural management practices; and
- Increased use of genetic resources without benefits-sharing.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

113. Regulation of genome-edited plants currently varies by jurisdiction. Some countries consider genome-edited plants to fall under the definition of "*living modified organism*" pursuant to the Cartagena Protocol on Biosafety regardless of the outcome of the genome editing process (e.g., single nucleotide variant or transgene), while other consider genome-edited plant to be equivalent to conventional varieties produced through traditional breeding (e.g., for those that do not result in the presence of transgenes). A mixed regulatory landscape may bring challenges to regulatory harmonization internationally, trade and thorough evaluation of the applications if risk assessment is not required. Further, regulatory considerations may need to be in place regarding the unintended incorporation of foreign DNA into the genome edited organism.

114. One of the main challenges for the regulation of genome-edited plants is related to detection and identification. Detection methods may not have the ability to distinguish between mutations caused from targeted mutagenesis and those resulting from natural mutation. Despite the developments with digital polymerase chain reaction and next-generation sequencing, detecting point mutations or the small addition or deletion of a few bases remains to be a technical challenge. Thus, analytical detection may need to be complemented by other enforcement measures, such as a voluntary registry for collection and dissemination of information.

115. However, other challenges related to genome edited plants may not be fundamentally different than those varieties produced through convention breeding techniques, depending on the trait introduced or enabled. Thus, regulation may need to be considered in proportion to the risks presented by the genome-edited plants, have different approaches depending on the plant species edited or be adaptable to further developments in science.

4. Additional relevant considerations

116. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, regulation, genome-edited plants could also raise additional relevant considerations. Some potential points may include:

- Improved nutrition and flavour of crops;
- Presence of unwanted secondary metabolites or toxic substances;
- Improved food security;
- Improved storage or increased shelf life;

- Improved development pipeline (e.g., increased breeding efficiency, increased availability of crop varieties, "orphan" and non-staple crops, expedited development pipeline);
- Responsible innovation (e.g., removal of varieties during development that do not meet performance or safety standards, lack of stable phenotypes);
- Due diligence by developer (e.g., ensuring no foreign DNA incorporation);
- Increased seed diversity;
- Increased economic benefits for farmers (e.g., higher yield and quality, increased productivity, cost savings);
- Public acceptance and perceptions;
- Intellectual property (e.g., ensuring access by breeders and farmers at affordable prices, preserving investment incentives, patenting of sequence from centres of origin);
- Access to technology for developing countries;
- Access to information and transparency (e.g., the need for a voluntary registry to improve traceability and information availability);
- Organic and "GMO-free" agriculture;
- Consumer choice and awareness; and
- Public engagement, including indigenous peoples and local communities.

F. Transient modification of agricultural plants, pests and pathogens using RNA interference or nanomaterials

117. Transient modification applications are generally based on the use of RNA interference to cause temporary gene silencing. The technology is based on the sequence homology between the double stranded RNA, hairpin RNA or small interfering RNA and a target messenger RNA. The double stranded RNA structure triggers a cellular response resulting in gene silencing through degradation of messenger RNA, blocking translation or inducing epigenetic changes (e.g., heterochromatin formation).

118. These applications can be formulated as topical sprays, which can be applied to crop plants, to feed or to food products to control pests and pathogens (biopesticides). However, the molecules can also be produced by living modified organisms containing a specific gene cassette, such as crop plants or cell factories, to confer pest resistance (e.g., by feeding) or enhance bioproduction (e.g., endogenous gene silencing). Thus, some applications aim to replace chemical pesticides.

119. Some specific examples of applications that could be considered as part of this item include:

- Topical applications targeting pest insects;
- Foliar sprays of double stranded RNA targeting pathogens on crops (e.g. Tobacco mosaic virus, fungi, viruses);
- Living modified maize expressing RNA interference cassette targeting corn rootworm;
- Living modified cassava expressing RNA interference cassette cassava brown streak disease; and
- Applications to control varroa mite in bee hives (e.g., double stranded RNA sugar solutions fed to bees to confer protection to worker bees).

120. Further, nanomaterials, such as clay nanosheets and biodegradable complexes, are investigated for improving double stranded RNA stability in the environment. These carriers may provide

protection from environmental nucleases and ultraviolet light. This is an active and complementary research area to the use of RNA interference-based biopesticides.

121. Transient modification of agricultural plants, pests and pathogens using RNA interference or nanomaterials may contribute to Targets 7 (Reduce Pollution to Levels That Are Not Harmful to Biodiversity) 10 (Enhance Biodiversity and Sustainability in Agriculture, Aquaculture, Fisheries, and Forestry) and 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) of the Kunming-Montreal Global Biodiversity Framework. However, RNA interference-based sprays could be considered to be pesticides, which may need further consideration in relation to Target 7, and biosafety safety measures may need strengthening to account for gaps in risk assessment and management to promote Target 17.

122. In addition, RNA interference -based application may also contribute to the United Nations Sustainable Development Goals 1(No Poverty), 2 (Zero Hunger), 3 (Good Health and Well-Being), 13 (Climate Action) and 15 (Life on Land). Furthermore, these applications may also support the Soil Conservation Strategy by the Food and Agriculture Organization of the United Nations and the Secretariat of the Convention on Biological Diversity.

1. Timeframe

123. RNA interference-based applications are immediate to near-term. Several LMOs containing RNA interference genetic cassettes have already been commercialized and approved in several jurisdictions (e.g., BPS-25271-9, DP-Ø23211-2, DP-3Ø5423-1, DPS-Ø4Ø46–8, MON-87411-9, MON-87429-9, MON-877Ø5-6 and MON-948Ø4-4).

124. Spray formulations containing double stranded RNA molecules are undergoing commercialization (e.g., Ledprona from GreenLight Biosciences, Evolutta Agro Biotecnologia and Sempre Agtech) in the United States of America and Brazil. Ledprona is expected to be the first dsRNA spray application for commercial use in plants. In other jurisdictions, such as China, field trials have been conducted. For example, Shanghai Zhi Sheng You Gu Biotechnology Co., Ltd. Performed tests of products against cotton aphids (*Aphis gossypii*), peach aphids (*Myzus persicae*) and striped flea beetles (*Phyllotreta striolata*). Further, Silray Technology (Shanghai) Co. have begin field testing their RNA interference biopesticides targeting nucleic acid interference factors against Tobacco mosaic virus. Other applications, such as those designed to alter the gender of prawns could also be in the process of commercialization, but it is not clear.

2. Potential impacts on the objectives of the Convention of Biological Diversity

125. The transient modification of agricultural plants, pests and pathogens using RNA interference or nanomaterials could have both positive and negative impacts on the objectives of the Convention on Biological Diversity.

126. Some potential positive impacts could include:

- Reduction of chemical, board-spectrum pesticides (e.g., reduced toxic exposure);
- Low toxicity;
- Specific targeting of pests and pathogens; and
- High environmental degradability.

127. Some potential negative impacts could include:

- Unintended impacts in off-target organisms when used in the environment;
- Unintended gene silencing within target organism;
- Changes in gene expression due to saturation of RNA interference machinery;
- Adverse immunological reactions;

- Persistence in environment (e.g., using novel formulations); and
- Novel forms of resistance development.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

128. When considering the use of transient modification applications, current regulatory frameworks, such the Cartagena Protocol on Biosafety, are likely sufficient support the process of risk assessment of LMO plants containing RNA interference cassettes. In contrast, since topical applications of double stranded RNA are not living organisms, they would not be considered to be subject to the provisions of the Cartagena Protocol on Biosafety. However, RNA interference-based biopesticides have also been assessed as chemical pesticide products by a few bodies, such as the Organization for Economic Cooperation and Development Working Party on Pesticides Ad Hoc Expert Group on RNA interference pesticides.

129. Despite this, potential challenges to risk assessment, risk management and regulation may still exist for transient modification applications. These may include:

- Stability of double stranded RNA molecules, particularly for novel formulations;
- Next-generation effects (e.g., intergenerational hereditary effects);
- Challenges to definition of "living modified organism" pursuant to the Cartagena Protocol on Biosafety if an organism is transiently modified;
- Treatment of topical applications as chemical pesticides (e.g., differing mode of action from conventional chemical pesticides);
- Exposure pathways of non-target organisms;
- Availability of suitable ecotoxicological testing;
- Limitations in the use of bioinformatic analyses for predicting off-targeting; and
- Lack of rapid and sensitive detection methods for measuring double stranded RNA molecules in the environment.

130. However, it can also be noted that due to the mechanism of RNA interference, there is no modification (i.e., sequence change) at the genome level for these products, even in a transient manner. Rather, gene silencing occurs at the level of transcription and translation.

4. Limits of knowledge

131. The use of transient modification applications in the environment may raise questions regarding current levels of knowledge in relation to the mode of action of these applications and could have implications on the risk evaluations of these application. Some potential considerations may include:

- Fate, kinetics and concentration of double stranded RNA molecules in the environment;
- RNA interference mechanism and specificity (e.g., organismal variation, homology considerations and size requirements of small interfering RNA to trigger an RNA interference response, response and epigenetic effects);
- Impact of polymorphisms and mutations on efficacy and impact of the application;
- Availability of genomic or transcriptomic sequences for all organisms in environment (e.g., prediction of possible off-target effects); and
- Unintended prolonged effects (e.g., epigenetic inheritance mechanisms).

5. Additional relevant considerations

132. In addition to the potential impact and challenges to risk assessment, transient modification of agricultural plants, pests and pathogens using RNA interference or nanomaterials could also raise additional relevant considerations. Some potential points may include:

- Alternative options to conventional pesticides (e.g., targeted pest control);
- Improved farm productivity (e.g., climate change mitigation);
- Human health (e.g., immunological reactions, sequencing homology to product, negligible impact due to physiology);
- Drift of dsRNA sprays to non-target fields or indigenous territories (e.g., co-existence with other production systems, liability, free, prior and informed consent);
- Ensuring access to the technology, particularly for developing countries (e.g., sharing benefits);
- Lack of knowledge sharing between the fields of health and agriculture regarding the use and exposure routes (e.g., oral intake);
- Intellectual property (e.g., extension to exposed organism and off-spring, claims on natural or agricultural systems); and
- Public and stakeholder participation (e.g., need for iterative communication processes).

G. Technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature

133. Advancements in synthetic biology can facilitate the modification of organisms in the field or in nature. These applications include novel mechanisms to deliver molecular machinery, vectors or double stranded RNA molecules to various target organisms without the need for tissue culturing or conventional transformation protocol. Specific example of advancements include.

134. Some specific examples of advancements include:

- Engineered gene drives;
- RNA interference topical applications;
- Horizontal Environmental Genetic Alteration Agents (e.g., insect delivery of viral sectors);
- Pollen-mediated delivery of genome editing machinery;
- Use of modified viruses (e.g., modified viruses to deliver genome editing machinery or induce RNA interference); and
- Use of nanoparticles and other novel chemistries (e.g., DNA nanotubules, engineered proteins).

1. Timeframe

135. Research and development of novel chemistries and new delivery systems was ongoing and nascent for certain applications. However, the modified phages targeting *Salmonella sp*. developed by Folium Science are undergoing commercialization in Brazil, Thailand and the United States (see section II, sub-section C above). In addition, double stranded RNA applications may also be in the near-future (see Section II, subsection F above), while engineered gene drives might be 5 to 10 years away for field testing (see Section I, sub-section C above).

2. Potential impacts on the objectives of the Convention of Biological Diversity

136. The technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature could have both positive and negative impacts particularly on the first objective of the Convention on Biological Diversity.

137. Some potential positive impacts on the conversation of biological diversity include:

- Reduced human damage on fragile ecosystems (e.g., use of engineered gene drives); and
- Reduced use of chemical pesticides (e.g., reduced toxic effects on biological diversity).

138. Some potential negative impacts on the conversation of biological diversity include:

- Disruption of evolutionary processes;
- Impaired biotic-biotic relationships;
- Off-target effects (such as in the case of genome editing, which could potentially cause genetic insertions, deletions, inversions, translocations and rearrangements);
- Horizontal gene transfer (e.g., spread of antibiotic resistance genes); and
- Unintended affects.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

139. When considering the technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature, potential challenges to risk assessment, risk management and regulation may exist. These could include:

- Lack of published risk assessments;
- Treatment of uncertainty;
- Lack of risk management measures (e.g., potential for irreversibility);
- Regulatory gaps (e.g., biosafety vs chemical regulatory mechanisms, potential for ‘grey’ area); and
- Labelling and traceability.

4. Limits of knowledge

140. Current knowledge surrounding the technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature could raise questions when used in the environment. Some considerations may include:

- Characterized microbial species in the environment (e.g., poor cultivation in laboratories for vast majority);
- Microbial interactions in the environment (e.g., microbial communities, host relationship); and
- Impact of cumulative effects.

5. Additional relevant considerations

141. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, and potential challenges to risk assessment, risk management and regulation, the technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature could also raise additional relevant considerations. Some potential points may include:

- Health (e.g., plasmid-mediated spread of antibiotic resistance genes to human-health relevant bacterial pathogens);

- Market concentration;
- Liability and redress (e.g., spread of application onto organic farm and subsequent legal status, damage to staple crops);
- Consumer choice (e.g., labelling);
- Dual-use; and
- Military funding (e.g., in the case of Horizontal Environmental Genetic Alteration Agents).

H. Ability to re-create viruses by chemical DNA synthesis[4]

142. Advancements in chemical DNA synthesis and assembly of oligonucleotides can allow for the de novo synthesis of viruses. To achieve infectious viral particles, oligonucleotides are first synthesized and then assembled into longer oligonucleotides based on overlapping homologous regions through the use of assembly strategies, such as polymerase chain reaction techniques, Gibson assembly, among other assembly or extension tools. These long oligonucleotides are then transfected into the appropriate host cell for replication and assembly of viral particles. Technological improvements have allowed for the use of fewer larger oligonucleotides (10 to 30 kilobases in size) for assembly, relied on synthetic genomics in yeast cells to assemble copy DNA and generate infectious RNA (for RNA viruses) and/or utilized helper viruses.

143. Some specific examples of viruses that have been re-created from synthetic oligonucleotide assembly include:

- Poliovirus;
- Bacteriophage φX174;
- Horsepox;
- Influenza (e.g., 1918 and H7N9 strains);
- Hepatitis C virus; and
- Coronaviruses (e.g., bat SARS-like coronavirus, SARS-CoV-2).

1. Timeframe

144. Proof of concept studies have occurred since the early 2000s. In 2000, researchers constructed a DNA copy of Hepatitis C virus and in 2002, researchers generated infectious polioviruses from DNA copies. Other significant examples include the synthesis of previously extinct influenza (1918 Spanish pandemic strain) in 2005 and horsepox virus in 2018.

145. Availability of viral sequence information (e.g., Virus Pathogen Database and Analysis Resource) and software tools to guide genome assembly processes may increase the speed of skilled researchers to assemble synthetic viral genomes. Increased capability of commercial nucleotide synthesis could also facilitate the assembly of synthetic RNA genomes (~30 kilobases) in a two to three week period by skilled researchers.

2. Potential impacts on the objectives of the Convention of Biological Diversity

146. Due to the development of these synthetic viruses in contained settings and for medical purposes, limited information regarding the potential impacts on the objectives of the Convention is available in published literature. However, there could be potential impacts on access and benefit sharing of genetic resources, such in the case of collecting genetic material from one nation to develop therapeutics without appropriate benefits sharing to the country of origin.

[4] Limited information was shared during the submissions process. Text under this section is based on Technical Series No. 100 and a limited number of references.

147. Regarding other potential impacts on the other objectives of the Convention, there is the potential for negative impacts if the technology is misused. However, if these applications are applied for other uses, there could also be potential positive impacts, such as the development of therapeutics for wildlife or animals.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

148. When considering the synthesis of viruses, potential gaps may relate to access and benefits sharing regulation, such as in the case of the Convention on Biological Diversity and the Nagoya Protocol. The availability of sequence information online and reduced costs of procuring synthetic oligonucleotides from a commercial provider could potentially allow for researchers to circumvent regulation. Other considerations may also include questions regarding containment and accidental release events, as well as the relationship between other international instruments, such as the Biological Weapons Convention for these applications.

4. Limits of knowledge

149. Limited information is available regarding the development of these applications in relation to the Convention on Biological Diversity.

5. Additional relevant considerations

150. Beyond the potential impacts to the objectives of the Convention on Biological Diversity, and potential challenges to risk assessment, risk management and regulation, the use of synthetic biology in wild organisms in the context of resilience in threatened species could also raise additional relevant considerations. Some potential points may include:

- Novel vaccine and gene therapy platforms;
- Rapid vaccine development;
- Creation of bioweapons;
- New pathogenic viruses (e.g., human pathogens);

151. However, it is important to note that viral genome assembly requires significant expertise to implement the required workflow and DNA synthesis companies have implemented a Harmonized Screening Protocol to voluntarily screen all orders in alignment with guidance from the US Department of Health and Human Services. While there is not a single DNA screening algorithm used by all IGSC members, DNA-screening software typically aligns a query sequence and 200 bp sub-sequences to a reference database of biological toxins and select agent genomes, genes, or proteins as a means of addressing biosecurity concerns associated with the potential misuse of their products to bypass existing regulatory controls.

I. Interaction of synthetic biology organisms in the environment and potential for cumulative effects

152. An increasing number of synthetic biology applications are enabled by new tools and techniques (e.g., new genome editing technologies), while also being produced due to convergences between various technological developments and fields. As such, individual impacts from each intervention could be combined together, leading to potential scale effects due to the numerous synthetic biology interventions, increased interactions and cumulative effects.

1. Timeframe

153. Cumulative and scale effects might already be occurring. However, these are expected to increase as new applications are rapidly developed and approved for release.

2. Potential impacts on the objectives of the Convention of Biological Diversity

154. The interaction of synthetic biology organisms in the environment and potential for cumulative effects is likely to impact the conservation and sustainable use of biological diversity objectives of the Convention on Biological Diversity.

155. The potential risks and impacts could be synergistic and/or non-linear, such as in the examples of the effect of large numbers observed in research on invasion ecology and the observations of cumulative effects from pesticide interventions. More specifically, synthetic biology organisms may compete with native species in the environment and the behaviour of the organisms out of containment could be unpredictable. Further, hybridization or mutation may further introduce adverse effects or reduce genetic diversity.

156. A better understanding of the interaction of synthetic biology organisms on the environment may facilitate a better understanding of interactions between species, providing insights in how to better manage and protect ecosystems. Further, there could also be novel conservation efforts, such as artificial ecosystems and gene banks, created to address damage caused by human activity.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

157. When considering the interaction of synthetic biology organisms in the environment and potential for cumulative effects, the challenges to risk assessment are likely related to the unpredictability of these interactions together (e.g., within the organism, between multiple organisms, hybridization), evolutionary factors and the behaviour of synthetic biology organisms in the environment, including interactions between multiple synthetic biology applications in the same environment. Biocontainment measures, such as “kill switches”, may assist in limiting impacts on biological diversity, but would likely require further research and development.

158. Given this, it would be important to foster interdisciplinary research and collaboration, including biology, environmental science, sociology, law and ethics, for informing risk assessment and regulation of synthetic biology applications. Additionally, there also could be a need for monitoring, particularly for unintended consequences (e.g., due to hybridization and evolution).

4. Additional relevant considerations

159. Similar to the experience with pesticides, cumulative effects may make the public cautious of synthetic biology-based interventions.

J. Transboundary movements and relation to detection and identification of synthetic biology organisms, parts and products

160. Ensuring the safe movement and detection and identification of the applications of synthetic biology could be important to prevent both unintended and illegal transboundary movements, as well as promote a positive public perception of the applications of synthetic biology. Thus, due to this importance, further work in the field of detection and identification of synthetic biology organisms and increased capacity-building is crucial.

161. Specific examples of applications that have a higher risk for unintentional transboundary movements, include those designed to spread (e.g., engineered gene drives).

1. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

162. In terms of regulation of synthetic biology applications that are considered to be LMOs, provisions exist in the Cartagena Protocol on Biosafety to manage transboundary movements. Further certain regional approaches, such as the Integrated Vector Management Platform in West Africa, support decision-making in a regional context by supporting the development of joint-guidelines for evaluating requests and capacity-building initiatives for vector control in the region.

163. Regarding the availability of tools for detection identification and monitoring of the applications of synthetic biology, establishing validated methods for detection and identification that can be used in very different organisms, appropriate identifiers, sampling strategies and detection limits are areas that may require further research and development. Establishing expert centres, improving access to information and investing in laboratory infrastructure may be able to address some of the needs with respect to detection and identification.

K. Increased field testing of synthetic biology applications, including in areas outside the national jurisdiction of the developer or funder

164. Field testing of synthetic biology applications is a precondition for wider release of these applications in the environment and following an extensive development phase in contained laboratory facilities. These trials are used to collect additional data and evaluating efficacy of the application outside contained conditions. Due to the transformative nature of synthetic biology, some applications aimed at addressing pressing issues in developing countries, field testing may occur outside the jurisdiction of the developer. However, field trials should be conducted in accordance with national legislation of a particular country and not related to the nationality of the developer.

1. Timeframe

165. Field trials for applications of synthetic biology were ongoing and likely to increase in number within the next 5 years.

2. Potential impacts on the objectives of the Convention of Biological Diversity

166. Field testing contributes to the conservation and sustainable use objectives of the Convention on Biological Diversity by generating information on potential impacts and ensuring biosafety risks can be appropriately managed. When field trials are conducted in areas where there is insufficient regulation or rule of law, biosafety risks may not be properly managed. Thus, in these cases, there could be a potential for negative impacts on biological diversity.

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

167. The major challenges to risk assessment and regulation would come from situations where field trials are conducted in areas where there is insufficient regulation or rule of law. In these cases, there is a greater potential for transboundary movements of synthetic biology applications. However, in situations where there are regulations, field testing would be conducted in accordance with national legislation.

L. Dual-use nature and biosecurity implications of synthetic biology

168. As the relevant technology becomes cheaper and more accessible, the potential for misuse or abuse of the technology could increase and warrant greater attention than before, especially when regulation might be missing, such as in the case for in many countries.

169. Applications based on microorganisms, such as synthetic biology bacteria and viruses, have a higher dual-use risk than those higher-level organisms, such as plants, animals. A bioterrorist would likely be more interested in creating novel pathogens for the organisms of interest. Thus, for certain applications deployed in animals and plants, such as engineered gene drives, short reproductive cycle would be required to have rapid effects.

170. The mis-use to dual-use of applications could have impacts on Targets 13 (Increase the Sharing of Benefits From Genetic Resources, Digital Sequence Information and Traditional Knowledge) and 17 (Strengthen Biosafety and Distribute the Benefits of Biotechnology) of the Kunming-Montreal Global Biodiversity Framework.

1. Timeframe

171. The timeframe for these impacts can vary widely, from immediate to years or decades, depending on specific applications, regulations and scientific advancements. Efforts are ongoing to address biosecurity concerns, requiring ongoing monitoring and policy adaptation. However, potential impacts may be realized within 5 to 10 year time period.

2. Potential impacts on the objectives of the Convention of Biological Diversity

172. The applications of synthetic biology could have both positive and negative impacts on the objectives of the Convention on Biological Diversity.

173. Some potential positive impacts on the conversation of biological diversity include:

- Tools to enhance our understanding of biodiversity and aid conservation efforts;
- Techniques to preserve and analyze genetic diversity of endangered species;
- Ecosystem restoration (e.g., de-extinction initiatives);
- Reduced resource use and support for sustainable agriculture (e.g., engineered crops);
- Reduced reliance on fossil fuels through the use of biofuels; and
- Facilitation of bioprospecting and benefit-sharing agreements.

174. Some potential negative impacts on the conversation of biological diversity include:

- Accidental release of engineered organisms that cause adverse ecological impacts;
- Exploitation of genetic resources without benefit-sharing; and
- Unintended consequences (e.g., development of novel pathogens).

3. Potential gaps to risk assessment, risk management and regulation, and availability of tools for detection, identification and monitoring

175. There could be a need to further consider the relationship between the dual-use of synthetic biology applications and existing international agreements, such as the Biological and Toxin Weapons Convention. Further, risk assessment models may not be fit to assess the risk resulting from mis-use of synthetic biology technologies. In addition, there could be challenges for some countries to monitor for such developments or uses.

4. Additional relevant considerations

176. The main consideration related to the dual-use nature of synthetic biology relates to misuse and bioterrorism due to a greater access enabling tools and technologies. However, other additional relevant considerations may also include:

- Expedited development of medicines and vaccines;
- Disputes over ownership and control over genetic resources if genetic information is synthesized or manipulated;
- Commercialization of genetic resources;
- Ethics (e.g., human intervention in nature);
- Public perception of synthetic biology; and
- Displacement of traditional industries and small-scale farmers.

Annex

Bibliographic references

I. Trends and issues identified for detailed assessment

A. Self-spreading vaccines for wildlife

Angulo, Elena, and Ben Gilna. When biotech crosses borders– international governance of self-dispersive GMOs purposefully released for public health, controlling invasive species and pests, and treating wildlife. *Nature Biotechnology*, vol. 26, No. 3 (March 2008), pp. 277–282.

Angulo, Elena, and Juan Bárcena. Towards a unique and transmissible vaccine against myxomatosis and rabbit haemorrhagic disease for rabbit populations. *Wildlife Research*, vol. 34 (July 2007), pp. 567–577.

Bakker, M. Kevin, and others. Fluorescent biomarkers demonstrate prospects for spreadable vaccines to control disease transmission in wild bats. *Nature Ecology & Evolution*, vol. 3 (November 2019), pp.1697–1704.

Bárcena, Juan, and others. Horizontal transmissible protection against myxomatosis and rabbit hemorrhagic disease by using a recombinant myxoma virus. *Journal of Virology*, vol. 74, No. 3 (February 2000), pp. 1114–1123.

Belgian Biosafety Server. Commercialisation of GMO medicinal products: Some figures. Available at https://www.biosafety.be/content/commercialisation-gmo-medicinal-products-some-figures. [Accessed 11 December 2023].

Brogna, Carlo, and others. Could SARS-COV-2 have bacteriophage behavior or induce the activity of other bacteriophages? *Vaccines*, vol. 10, No. 5708 (April 2022).

Browne, Malcolm W. New Animal Vaccines Spread Like Diseases. The New York Times, available at https://www.nytimes.com/1991/11/26/science/new-animal-vaccines-spread-like-diseases.html.

Bull, James J. Transmissible Viral Vaccines. *Trends in Microbiology*, vol. 26, No. 1 (January 2018), pp. 6–15.

C. M. Hardy, CM, and others. Biological of vertebrate pests using virally vectored immunocontraception. *Journal of Reproductive Immunology*, vol. 71, No. 2 (October 2006), pp. 102–111.

Cayetano, Shari Messinger, and Lee Crandall. The paradox of success and public perspective: COVID-19 and the perennial problem of prevention. *Journal of Epidemiology & Community Health*, vol. 74, No. 8 (2020).

Church, George M., and Edward Regis. Regenesis: How synthetic biology will reinvent nature and ourselves. New York: Basic Books, 2012.

Cogley, Michael. Could self-spreading vaccines stop a coronavirus pandemic? The Telegraph, 31 January 2020, available at https://www.telegraph.co.uk/technology/2020/01/28/could-self-spreading-vaccines-stop-global-coronavirus-pandemic/.

De Figueiredo, Alexandre, and others. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: A large-scale retrospective temporal modelling study, *The Lancet*, vol. 396 No. 10255 (September 2022), pp. 898–908.

Dickinson, Demetria. Transmissible and transferable Vaccines. Technology networks, 3 May 2022.

Doudna, Jennifer A., and Samuel H. Sternberg. *A Crack in creation: Gene editing and the unthinkable power to control evolution*. Boston, Houghton Mifflin, Harcourt, 2017.

European Environment Agency. Late lessons from early warnings: Science, precaution, innovation. No. 1/2013. Luxembourg: Publications Office of the European Union, 2013.

_____. Late lessons from early warnings: The precautionary principle 1896-2000. No. 22. Luxembourg: Office for Official Publications of the European Communities, 2001.

European Food Safety Authority Scientific Committee, and others. Scientific Opinion on the evaluation of existing guidelines for their adequacy for the microbial characterisation and environmental risk assessment of microorganisms obtained through synthetic biology. *EFSA Journal*, vol. 18, No. 10 (October 2020).

Germany, Federal Agency for Nature Conservation. 2013 Nature Awareness Study: population survey on nature and biological diversity. Berlin: Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety, 2013.

_____. Genetic engineering, nature conservation and biological diversity: The boundaries of design (2022). Available at https://doi.org/10.19217/pos222.

Griffiths, Megan E., and others. Inferring the disruption of rabies circulation in vampire bat populations using a betaherpesvirus-vectored transmissible vaccine. *Proceedings of the National Academy of Sciences*, vol. 120, No. 11 (March 2023).

Hansen, Frederic, and others. Isolation and genome sequencing of cytomegaloviruses from Natal multimammate mice (Mastomys natalensis). *The Journal of General Virology*, vol. 104, No. 8 (August 2023).

Henderson, Wendy R., and Elaine C. Murphy. Pest or prized possession? Genetically modified biocontrol from an international perspective. *Wildlife Research*, vol. 34, No. 7 (December 2007), pp. 578–585.

Lentzos, Filippa, and others. Eroding norms over release of self-spreading viruses. *Science*, vol. 375, No. 6576, (January 2022), pp. 31–33.

_____. Self-spreading vaccines: Base policy on evidence–Response. *Science*, vol. 375, No. 6587 (March 2022).

Mackenzie, S.M., and others. Immunocontraceptive effects on female rabbits infected with recombinant myxoma virus expressing rabbit ZP2 or ZP3. *Biology of Reproduction*, vol. 74, No. 3 (March 2006), pp. 511–21.

Manemann, Jurgen. Kritik des Anthropozäns. Plädoyer für eine neue Humanökologie transcript. 2014. Available at https://www.transcript-verlag.de/978-3-8376-2773-2/kritik-des-anthropozaens/.

Meyer-Abich, Klaus Michael. Praktische Naturphilosophie: Erinnerung an einen vergessenen Traum. Munich: C. H. Beck, 1997.

Mueller, Siguna Mueller. Potentials of Pathogen Research Through the Lens of Cyberbiosecurity, or What Threat Actors Can Learn from the Covid-19 Pandemic. Switzerland, Springer Nature, 2023.

_____. Recombination between coronaviruses and synthetic RNAs and biorisk implications motivated by a SARS-CoV-2 FCS origin controversy. *Frontiers in Bioengineering and Biotechnology*, vol. 11 (August 2023).

_____. Challenges and Opportunities of mRNA Vaccines Against SARS-CoV-2 – A Multidisciplinary Perspective. Springer, 2023.

New Zealand Harold. GE carrots could clobber possums, 6 November 2011. Available at https://www.nzherald.co.nz/nz/ge-carrots-could-clobber-possums/MENTTBBDUFLGLRBCW3XSVQMFGQ/.

Nuismer, Scott L., and Bull, James J. Self-disseminating vaccines to suppress zoonoses. *Nature Ecology & Evolution*, vol. 4 (July 2020), pp. 1168–1173.

Nuismer, Scott L., and others. Controlling epidemics with transmissible vaccines. *PLOS ONE*, vol. 13, No. 5 (May 2018).

Nuismer, Scott L., and others. Eradicating infectious disease using weakly transmissible vaccines. *Proceedings of the Royal Society B*, vol. 283, No. 1841 (October 2016).

Nuismer, Scott L., and others. Evolution and containment of transmissible recombinant vector vaccines. *Evolutionary Applications*, vol. 12, No. 8 (September 2019), pp. 1595–1609.

PREEMPT. Big win new countermeasures to eliminate pandemic risk. Available at [https://static1.squarespace.com/static/5d927ef93f54836cb17542c1/t/5e74072e6f3a42255b9573fe/1584662333204/BIG+WIN-New+Countermeasures.pdf].

Preston, J. Christopher. the synthetic age: outdesigning evolution, resurrecting species, and reengineering our world, The MIT Press, 2018).

Proactive Investors. The vaccine group completes two deadly disease vaccination projects, YouTube video, 12 January 2023. Available at https://www.youtube.com/watch?v=KHFjabspTcM.

Redwood, Alec J., and others. Prospects for virally vectored immunocontraception in the control of wild house mice (Mus domesticus). *Wildlife Research*, vol. 34, No. 7 (December 2007).

Rella, Simon A., and others. Rates of SARS-CoV-2 transmission and vaccination impact the fate of vaccine-resistant strains. *Scientific Reports*, vol. 11, No. 15729 (July 2021).

Rocke, Tonie E., and others. Virally-vectored vaccine candidates against white-nose syndrome induce anti-fungal immune response in little brown bats (*Myotis lucifugus*). *Science Reports*, vol. 9, No. 6788 (May 2019).

Ross, D. W., Infectious vaccines. *Archives of Pathology & Laboratory Medicine*, vol. 122, No. 1(January 1998), pp. 100–101.

Sandbrink, B. Jonas, and others. Safety and security concerns regarding transmissible vaccines. *Nature Ecology & Evolution*, vol. 5, No. 4 (February 2021), pp. 405–406.

Braverman, Iris. *Gene Editing, Law, and the Environment*. 1st ed. Routledge, 2017.

Sandler, Ronald. The ethics of genetic engineering and gene drives in conservation. Conservation Biology, vol. 34, No. 2 (2019), pp. 378–385.

Sattar, Sarah, and others. Nuclear translocation of spike mRNA and protein is a novel feature of SARS-CoV-2. *Frontiers in Microbiology*, vol. 14 (January 2023).

Schreiner L., Courtney, and others. Optimizing the delivery of self-disseminating vaccines in fluctuating wildlife populations. *PLOS Neglected Tropical Diseases*, vol. 17, No. 8 (August 2023).

Scudellari, Megan. Journal Club: Can transmissible vaccines have a major role in eradicating disease?. *PNAS*, 14 November 2016. Available at https://blog.pnas.org/2016/11/journal-club-can-transmissible-vaccines-have-a-major-role-in-eradicating-disease/.

Streicker, G., Daniel, James J. Bull, and Scott L Nuismer. Self-spreading vaccines: Base policy on evidence. *Science*, vol. 375, No. 6587, (March 2022), pp. 1362–1363.

The Vaccine Group. Our strategy is to develop herpesvirus-based vaccines for use in animals to protect against infectious disease. Available at https://thevaccinegroup.com/science/. [Accessed 11 December 2023].

_____. Pipeline. Available at https://thevaccinegroup.com/pipeline/.

_____. TVG successfully completes DARPA-funded transmissible Lassa fever vaccine project. 5 December 2022.

Then, Christoph. Gentechnik gefährdet den Artenschutz, *Testbiotech and Deutscher Naturschutzring*, November 2010. Available at https://www.testbiotech.org/content/gentechnik-artenschutz.

Toepfer, George. Artenschutz durch Gentechnik? *Natur und Landschaft*, vol. 95, No. 5 (2020), pp. 220–225.

Torres, M. Juan, and others. First field trial of a transmissible recombinant vaccine against myxomatosis and rabbit hemorrhagic disease. *Vaccine*, vol. 19, No. 31, (August 2001), pp. 4536–4543.

Transmissible Vaccines. Coordinating the development of self-disseminating vaccines for spillover prevention. Available at https://transmissiblevaccines.org/workshop-dev-vaccines/.

Tsuda, Yoshimi, and others. A replicating cytomegalovirus-based vaccine encoding a single ebola virus nucleoprotein CTL epitope confers protection against ebola virus. *PLoS Neglected Tropical Diseases*, vol. 5, No. 8, (August 2011).

United nations, Convention on Biological Diversity. *Report of the Canada-Norway expert workshop on risk assessment for emerging applications of living modified organisms*. UNEP/CBD/BS/COP-MOP/4/INF/13. 17 July 2013. Available at https://www.cbd.int/kb/record/meetingDocument/58217?RecordType=meetingDocument&Event=BSRARM-01.

United States of America, Animal and Plant Health Inspection Service. Availability of an Environmental Assessment for Field Testing of a Pseudogymnoascus destructans Vaccine, Live Raccoon Poxvirus Vector (RCN-CAL/SP). Washington, DC, 2023. Available at https://www.regulations.gov/docket/APHIS-2019-0043/document.

_____. Environmental Assessments; Availability, etc.: Field Testing of a Pseudogymnoascus destructans Vaccine, Live Raccoon Poxvirus Vector. Washington, DC, 2 August 2019. Available at https://www.regulations.gov/document/APHIS-2019-0043-0001.

University of California Davis. $9M to preempt zoonotic spillover threats, protect military and local communities. Available at https://www.ucdavis.edu/news/9m-preempt-zoonotic-spillover-threats-protect-military-and-local-communities.

_____. PREEMPT. Available at https://www.preemptproject.org/about. [Accessed 10 December 2023].

Van Der Vlugt, J.B Cécile. Horizon Scan of Synthetic Biology Developments for Microorganisms with application in the Agri- Food Sector. *EFSA Supporting Publications*, vol. 17, No. 3 (March 2020).

Weinberger, Leor S. A Gene Drive Therapy for HIV: single-administration intervention for high-risk groups. Grantome National Institutes of Health. Available at https://grantome.com/grant/NIH/DP1-DA051144-01.

World Health Organization. Health topics-Rabies. Available at https://www.who.int/health-topics/rabies. [Accessed 11 December 2023].

_____. *WHO Informal Consultation on Reproductive Control of Carnivores*. Geneva, 16 June 1993. Available at https://iris.who.int/handle/10665/60995.

Ynga-Durand, Mario Alberto, Iryna Dekhtiarenko, and Luka Cicin-Sain. Vaccine vectors harnessing the power of cytomegaloviruses. *Vaccines*, vol. 7, No. 4, (October 2019).

B. Development of engineered gene drives to control vector-borne diseases and invasive species

African Centre for Biodiversity. *The financialization of malaria in Africa: Burkina Faso, rogue capital & GM /gene drive mosquitoes*. 28 April 2022. Available at https://acbio.org.za/corporate-expansion/financialisation-of-malaria-in-africa.

African Union Development Agency. *Gene Drives for Malaria Control and Elimination in Africa.* Johannesburg, South Africa. Available at https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa.

_____. *Guidelines for Compliance Monitoring and Inspection of Activities involving Genetically Modified Mosquitoes*. Johannesburg, South Africa, 2022.

_____. Guidelines for Risk Analysis for the Testing and Deployment of Genetically Modified Mosquitoes. Johannesburg, South Africa, 2022.

Antia, Mfoniso, Save our Seeds. Gene Drives: exploiting the lack of awareness. YouTube video, 31 October 2022.

Arnim von Gleich and Winfried Schröder, eds. *Gene drives at tipping points: Precautionary technology assessment and governance of new approaches to genetically modify animal and plant populations*. Cham: Springer International Publishing, 2020.

Australian Academy of Science. Discussion Paper Synthetic Gene Drives in Australia: Implications of Emerging Technologies. May 2017.

_____. Synthetic gene drives in Australia: implications of emerging technologies. May 2017, Available at https://www.science.org.au/support/analysis/reports/synthetic-gene-drives-australia-implications-emerging-technologies.

Barat, Lawrence M. Four malaria success stories: how malaria burden was successfully reduced in Brazil, Eritrea, India, and Vietnam. *The American journal of tropical medicine and* hygiene, vol.74, No. 1 (January 2006), pp.12–16.

Bartimaeus, Frederic, and others. Sustainable Innovation in Vector Control Requires Strong Partnerships with Communities. *PLOS Neglected Tropical Diseases*, (April 2019).

Boëte, Christophe. Letter: Gene Drive and Trust in Science. *Genewatch: a bulletin of the Committee for Responsible Genetics*, vol. 31, No. 1 (July 2018), pp. 18–19.

Braverman, Iris. *Gene Editing, Law, and the Environment*. 1st ed. Routledge, 2017.

Buchori, Damayanti, and others. Risk Assessment on the Release of Wolbachia-Infected Aedes aegypti in Yogyakarta, Indonesia. *Insects*, vol. 13, No. 10 (October 2022), pp. 924.

Bull, J.J. Lethal Gene Drive Selects Inbreeding. *bioRxiv*, (June 2016).

Castro, Marcia C. Malaria Transmission and Prospects for Malaria Eradication: The Role of the Environment. *Cold Spring Harbor perspectives in Medicine*, (May 2017).

Champer, Jackson, and others. Suppression gene drive in continuous space can result in unstable persistence of both drive and wild-type alleles. *Molecular Ecology*, vol. 30, No. 4 (January 2021), pp. 1086–1101.

Chemonges, Elinor W., and others. Co- developing a Common Glossary with Stakeholders for Engagement on New Genetic Approaches for Malaria Control in a Local African Setting. *Malaria Journal*, vol. 20, No. 1 (January 2021).

Ching, Lim Li, and Lim Li Lin. *Gene Drives, legal and regulatory Issues*. Third World Network. Penang, Malaysia, 2019.

Christopher Bendana. Anti -GM activists target Malaria Eradication Program in Uganda. *Sciencenow*, (October 2023).

Coate, David J., and others. Genetic Diversity and Conservation Units: Dealing with the Species-Population Continuum in the Age of Genomics. *Frontiers in Ecology and Evolution*, vol. 6, No. 165 (October 2018).

Connolly, John B., and others. Gene drive in species complexes: defining target organisms. *Trends in Biotechnology*, vol. 41, No. 2, (February 2023), pp. 154–164.

Connolly, John B., and others. 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. *Malaria Journal*, vol. 20, No. 170 (March 2021).

Cook, Carly N., and others. Species Conservation in the Era of Genomic Science. *BioScience*, (November 2023).

Courtier-Orgogozo, Virginie, and others. Agricultural pest control with CRISPR-based gene drive: time for public debate. *EMBO Reports*, vol. 18, No. 6 (May 2017), pp. 878–880.

Courtier-Orgogozo, Virginie, and others. Evaluating the Probability of CRISPR-Based Gene Drive Contaminating Another Species. *Evolutionary applications*, vol. 13, No. 8 (September 2020), pp. 1888–1905.

Critical Scientists Switzerland, Vereinigung Deutscher Wissenschaftler & European Network of Scientists for Social and Environmental Responsibility. *Gene Drives: A Report on Their Science, Applications, Social Aspects, Ethics and Regulations*. May 2019. Available at https://genedrives.ch/report.

David, Aaaron S., and others. Release of genetically engineered insects: a framework to identify potential ecological effects. *Ecology and Evolution*, vol. 3, No. 11 (October 2013), pp. 4000–4015.

Devos, Yann, and others. Potential use of gene drive modified insects against disease vectors, agricultural pests and invasive species poses new challenges for risk assessment. *Critical Reviews in Biotechnology*, vol. 42, No. 2 (June 2021), pp. 254–270.

Dolezel, Marion, and others. Beyond limits – the pitfalls of global gene drives for environmental risk assessment in the European Union. *BioRisk*, vol. 15 (May 2020) pp. 1–29.

E. Helen Roy, and others. IPBES Invasive Alien Species Assessment: Summary for Policymakers. *IPBES*, vol. 3 (November 2023).

EFSA Panel on Genetically Modified Organisms. Guidance on the environmental risk assessment of genetically modified plants. *EFSA Journal*, vol. 8, No. 11 (November 12, 2010).

Ellstrand, Norman C., and others. Introgression of Crop Alleles into Wild or Weedy Populations, Annual Review of Ecology. *Evolution and Systematics*, vol. 44 (November 2013), pp. 325–345.

Emerson, Claudia, and others. Principles for gene drive research. *Science*, vol. 358, No. 6367 (December 1, 2017), pp. 1135–1136.

Environment Agency Austria. *Gene Drive Organisms: Implications for the environment and nature conservation.* Available at https://www.umweltbundesamt.at/fileadmin/site/publikationen/rep0705.pdf.

ETC Group. Forcing the Farm: How Gene Drive Organisms Could Entrench Industrial Agriculture and Threaten Food Sovereignty, October 2018.

European Environment Agency. Late Lessons from Early Warnings: Science, Precaution, Innovation. Copenhagen, 2013.

_____. Late lessons from early warnings: the precautionary principle 1896–2000. Copenhagen, 2013.

European Group on Ethics in Science and New Technologies. *Ethics of Genome Editing*, European Commission, Brussels, 2021.

European Parliament. EU Biodiversity Strategy for 2030: Bringing Nature Back into Our Lives – Closing Statement by Virginijus Sinkevičius. European Commissioner for Environment, 2021.

_____. The role of development policy in the response to biodiversity loss in developing countries, in the context of the achievement of the 2030 Agenda. Strasbourg, 2020.

European Union. European Parliament resolution of 16 January 2020 on the 15th meeting of the Conference of Parties (COP15) to the Convention on Biological Diversity (2019/2824(RSP)).

Evans, Benjamin R., and others. Transgenic *Aedes aegypti* Mosquitoes Transfer Genes into a Natural Population. *Scientific Reports*, vol. 9, No.13047 (September 2019).

Ferraz, José Maria Gusman, Save our seeds. Q1. Circumstances of the Release of Oxitec's GMO Mosquitos in Brazil, YouTube video, 6 December 2022.

Ferraz, José Maria Gusman, Save our Seeds. Q10. Oxitec's GM Mosquitos Persistence in the Environment, YouTube video, 6 December 2022.

Frieß, Johannes L, and others. Review of gene drive modelling and implications for risk assessment of gene drive organisms. *Ecological Modelling*, vol. 478, No. 110285 (April 2023).

GeneWatch UK. *Oxitec's failed GM mosquito releases worldwide: Forewarnings for Africa and the Target Malaria project*. Third World Network, Available at http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/Oxitec_failed_GM_mosquito_releases_worldwide_Forewarnings_for_Africa_and_the_Target_Malaria_project.pdf.

George, Dalton R., and others. Articulating 'free, prior and informed consent' (FPIC) for engineered gene drives. *Proceedings of the Royal Society B: Biological Sciences*, vol. 286, No. 1917 (December 2019).

Germany, Federal Agency for Nature Conservation. *Genetic Engineering, Nature Conservation and Biological Diversity*. Bundesamt für Naturschutz, Bonn, 2022.

Gierus, Luke, and others. Leveraging a natural murine meiotic drive to suppress invasive populations. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 119, No. 46 (November 2022).

Godwin, John, and others. Rodent gene drives for conservation: opportunities and data needs. *Proceedings of the Royal Society B: Biological Sciences*, vol. 286, No. 1914, (November 2019).

Hammond, Andrew, and others. The Creation and Selection of Mutations Resistant to a Gene Drive over Multiple Generations in the Malaria Mosquito. *PLoS Genetics*, vol. 13, No. 10 (October 2017).

Harry, Debra. Save our Seeds. Gene Drives: extending the patterns of colonisation, YouTube video, 22 September 2022.

Hefferon, Kathleen, and Ronald Herring. Engineered Gene Drives and their Value in the Control of Vector-Borne Diseases, Weeds, Pests, and Invasive Species. vol. 19 (December 2020), pp. 401–419.

International Union for Conservation of Nature (IUCN). *Genetic frontiers for conservation: An assessment of synthetic biology and biodiversity conservation*. Gland, Switzerland, 2019. Available at https://portals.iucn.org/library/efiles/documents/2019-012-En.pdf.

James, Stephanie L., and others. Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing. *Vector-Borne and Zoonotic Diseases*, vol. 20, No. 4 (March 2020), pp. 237–251.

Justo-Hanani, Ronit and Tamar Dayan. Risk regulation and precaution in Europe and the United States: the case of bioinvasion. *Policy Sciences*, vol. 54, No. 4 (May 2020), pp. 3–20.

_____. Environmental policy expansion in the EU: The intriguing case of bioinvasion regulation. *Journal of Environmental Policy & Planning*, vol. 22, No. 3 (December 2021), pp. 315–327.

Kolopack, Pamela A., and James V. Lavery. Informed Consent in Field Trials of Gene-Drive Mosquitoes. *Gates Open Research*, (2017).

Lim Li Ching. *Synthetic Biology and Relevant international Law*. Third World Network Biotechnology and biosafety series 18. Jutaprint, Penang, Malaysia, 2017.

Louda, S. M., and others. Nontarget effects--the Achilles' heel of biological control? Retrospective analyses to reduce risk associated with biocontrol introductions. *Annual Review of Entomology*, vol. 48 (2003), pp. 365–396.

Macer, Darryl. Ethical, legal and social issues of genetically modifying insect vectors for public health. *Insect Biochemistry and Molecular Biology*, vol. 35, No. 7 (July 2005), pp. 649–660.

Manana Pinky N., and others. Maskandi experience: exploring the use of a cultural song for community engagement in preparation for a pilot Sterile Insect Technique release programme for malaria vector control in KwaZulu-Natal Province, South Africa 2019. *Malaria Journal*, vol. 20, No. 204 (April 2021).

Matoke-Muhia, Damaris, and Emma Orefuwa. Enhancing Women's Role in the Control of Vector-Borne Diseases. Pan-African Mosquito Control Association, Nairobi Kenya. Available at https://www.pamca.org/en/projects/view/2/enhancing-women%E2%80%99s-role-in-the-control-of-vector-borne-diseases.

McLaren Duncan, and Nils Markusson. The co-evolution of technological promises, modelling, policies and climate change targets. *Nature Climate Change*, Vol. 10, No. 5 (April 2020), pp. 1–6.

Meurisse, N., and others. Risk Analysis Frameworks Used in Biological Control and Introduction of a Novel Bayesian Network Tool. *Risk Analysis*, vol. 42 (August 2021), pp. 1255–1276.

Michelle A. E. Anderson, and others. Closing the gap to effective gene drive in Aedes aegypti by exploiting germline regulatory elements. *Nature Communications*, vol. 14, No. 338 (January 2023)

Milius, Susan. Mosquitoes may surf winds above Africa more than we realized. *Science News*, (November 2018). Available at https://www.sciencenews.org/article/mosquitoes-winds-africa-sahel-malaria.

Molina-Cruz, Alvaro, and Carolina Barillas-Mury. The remarkable journey of adaptation of the Plasmodium falciparum malaria parasite to New World anopheline mosquitoes. *Mem Inst Oswaldo Cruz*, vol. 109, No. 5 (August 2014), pp. 662–667.

Msugupakulya, Betwel J., and others. Changes in contributions of different Anopheles vector species to malaria transmission in east and southern Africa from 2000 to 2022. *Parasites & Vectors*, vol. 16, No. 408. (November 2023).

Murray, Justine V., and others. Risk Associated with the Release of Wolbachia-Infected Aedes aegypti Mosquitoes into the Environment in an Effort to Control Dengue. *Public Health*, vol. 4 (2016).

National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*. Washington, D.C.: The National Academies Press, 2016.

Noble, Charleston, and others. Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife*, vol. 7, No. 33423 (June 2018).

Norwegian Biotechnology Advisory Board. *Statement on gene drives*, 14 February 2017.

Office of Technology Assessment at the German Bundestag. *Gene drives – technologies for propagating genetic modifications throughout populations*. Available at https://www.tab-beim-bundestag.de/english/projects_gene-drives-technologies-for-propagating-genetic-modifications-throughout-populations.php.

Olivera, Mario J., and others. Socioeconomic determinants for malaria transmission risk in Colombia: An ecological study. *Microbes, Infection and Chemotherapy*, vol. 2 (April 2022).

Olivia, Clélia F., and others. Sterile Insect Technique (SIT) against Aedes Species Mosquitoes: A Roadmap and Good Practice Framework for Designing, Implementing and Evaluating Pilot Field Trials. *Insects*, vol. 12, No. 3 (February2021), pp. 191.

Otto, Mathias, and others. Genetic modification of wild populations - nature's edited version? *Natur und Landschaft, (*May 2020).

Oye, Kenneth A., and others. Regulating gene drives. *Science*, vol. 345, No. 6197 (August 2014), pp. 626–628.

Paul Neve. Gene drive systems: do they have a place in agricultural weed management? *Pest Management Science*, vol. 74, No. 12 (2018), pp. 2671–2679.

Pollegioni, Paola, and others. Introgression of a synthetic sex ratio distortion transgene into different genetic backgrounds of *Anopheles coluzzii*. *Royal Entomology Society*, vol. 32, No. 1 (October 2022), pp. 56–58.

Quagliata, Michael, and others. Malaria vaccines. *Expert Opinion on Therapeutic* Patents, vol. 33, No. 3 (March 2023), pp.169–178.

Raban, Robyn R. Raban, and others. Progress towards engineering gene drives for population control. *Journal of Experimental Biology*, vol. 223, No. 1 (February 2020).

Rabitz, Florian. Gene drives and the international biodiversity regime. *Reciel*, vol. 28, No. 3 (November 2019), pp. 339–348.

Rašić, Gordana, and others. Monitoring needs for gene drive mosquito projects: lessons from vector control field trials and invasive Species. *Frontiers in genetics*, vol. 12 (January 2022).

Reed, Floyd A. CRISPR/Cas9 Gene Drive: Growing Pains for a New Technology. *Genetics*, vol. 205, No. 3 (March 2017), pp. 1037–1039.

Resnik, David B. Ethical Issues in Field Trials of Genetically Modified Disease-Resistant Mosquitoes. *Dev World Bioeth*, vol. 14, No. 1 (December 2012) pp. 37–46.

Roberts, Aaron J., and Delphine Thizy. Articulating Ethical Principles Guiding Target Malaria's Engagement Strategy. *Malaria Journal*, vol. 21, No. 35 (February 2022).

Romeis, Jörg, and others. The value of existing regulatory frameworks for the environmental risk assessment of agricultural pest control using gene drives. *Environmental Science & Policy*, vol. 108 (June 2020), pp. 19–36.

Sandler, Ronald. The ethics of genetic engineering and gene drives. *Conservation Biology*, vol. 34, No. 2 (August 2019), pp. 378–385.

Santos, Michael R. Evaluating Gene Drive Approaches for Public Benefit. *in Topics in Biodiversity and Conservation*, vol. 19, (Springer, 2020).

Scott, Maxwell J., and others. Agricultural production: assessment of the potential use of Cas9-mediated gene drive systems for agricultural pest control. *Journal of Responsible Innovation*, vol. 5, (2018), pp. 98–120.

Shannon, Xiang-Rum, and others. Active Genetic Neutralizing Elements for Halting or Deleting Gene Drives. vol. 80, No. 2 (September 2020), pp. 246–262.

Simon, Samson, and others. Synthetic gene drive: Between continuity and novelty: Crucial differences between gene drive and genetically modified organisms require an adapted risk assessment for their use. *EMBO reports*, vol. 19, No. 5 (April 2018).

Stop gene drives. Can gene drives spread between mosquito species? 26 September 2022. Available at https://www.stop-genedrives.eu/en/can-gene-drives-spread-between-mosquito-species/.

Taitingfong, Riley L. Islands as Laboratories: Indigenous Knowledge and Gene Drives in the Pacific. *Human Biology*, vol. 91, No. 3 (June 2020), pp. 179–188.

_____. Save our Seeds. Gene Drives: the missing perspectives. YouTube video, 7 October 2022.

Target Malaria, about us. Available at https://targetmalaria.org

Teem, John L., and others. Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018. *Malaria Journal*, vol. 18, No. 347, (October 2019).

TestBioTech. Submission of information and supporting documentation relevant to risk assessment of gene drives, 2 April 2023.

The Anopheles gambiae 1000 Genomes Consortium. Natural diversity of the malaria vector *Anopheles gambiae. bioRxiv,* No. 096289 (December 2016).

Then, Christoph, Katharina Kawall, and Nina Valenzuela. Spatiotemporal Controllability and Environmental Risk Assessment of Genetically Engineered Gene Drive Organisms from the Perspective of European Union Genetically Modified Organism Regulation. *Integrated Environmental Assessment and Management*, vol. 16, No. 5 (September 2020), pp. 555–568.

Then, Christoph, Arnim von Gleich, and Winfried Schröder (eds). *Limits of knowledge and tipping points in the risk assessment of gene drive organisms*. Springer Nature, Switzerland, 2020.

Thogmartin, Wayne E., and others. Monarch butterfly population decline in North America: identifying the threatening processes. *Royal Society Open Science*, vol. 4, No. 9 (September 2017).

Tiedje, James M., and others. The Planned Introduction of Genetically Engineered Organisms: Ecological Considerations and Recommendations. *Ecology*, vol. 70, No. 2 (April 1989), pp. 298–315.

Unckless, Robert L., and others. Evolution of Resistance Against CRISPR/Cas9 Gene Drive. *Genetics*, vol. 205, No. 2 (February 2017), pp. 827–841.

United Nations, Convention on Biological Diversity. *Summary of discussions of the open-ended online forum on synthetic biology*. SYNBIO/AHTEG/2023/1/INF/2, 11-13 July 2023.

_____. Biosafety Technical Series 05: Training Manual on the Detection and Identification of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety. April 2022.

United States of America, United States Environmental Protection Agency. *Human Health and Environmental Risk Assessment of OX5034 Aedes aegypti Containing Tetracycline-Repressible Transactivator Protein Variant (tTAV-OX5034, new active ingredient), DsRed2-OX5034 Protein (new inert ingredient), and the genetic material necessary (Vector pOX5034) for production of the proteins in vivo. Data and information provided in support of an extension and amendment to a FIFRA Section 5 experimental use permit for testing in Florida and California.* 2022.

_____, Environmental Protection Agency. *EPA Approves Experimental Use Permit to Test Innovative Biopesticide Tool to Better Protect Public Health.* Washington, DC, 2020.

_____, Food and Drug Administration, *Draft Environmental Assessment and Preliminary Finding of No Significant Impact Concerning Investigational Use of Oxitec OX513A Mosquitoes; Availability.* Washington, DC, 2016.

University of California Malaria Initiative. Population-Modification Approach. Stop Malaria. Available at https://stopmalaria.org/.

Vella, Michael R., and others. Evaluating strategies for reversing CRISPR-Cas9 gene drives. *Nature Scientific Reports*, vol. 7, No. 11038 (September 2017).

Vitale Matteo, and others. Comprehensive characterization of a transgene insertion in a highly repetitive, centromeric region of Anopheles mosquitoes. *Pathogens and Global Health*, vol. 117, No. 3 (July 2022), pp. 273–283.

Wells, Mark, and Ricarda A. Steinbrecher. Current and proposed insect targets for gene drive development. EcoNexus, October 2023.

World Health Organization, *Global technical strategy for malaria 2016-2030*. Geneva, 2015. Available at https://iris.who.int/handle/10665/176712.

_____. Vector Control Advisory Group, *Seventeenth meeting of the WHO Vector Control Advisory Group: Meeting report.* Geneva, October 2022.

_____. WHO urges increased implementation of recommended tools to combat malaria. News Release, April 2023.

C. Self-limiting insect systems

Adama, Franck Yao, and others. Mark-release-recapture experiment in Burkina Faso demonstrates reduced fitness and dispersal of genetically-modified sterile malaria mosquitoes. *Nature Communications*, vol. 13, No. 796 (10 February 2022).

Alphey, Luke S., and others. Opinion: Standardizing the definition of gene drive. *Proceedings of the National Academy of Sciences USA*, vol. 117, No. 49 (November 2020), pp. 30864–30867.

Ant, Thomas, and others. Control of the olive fruit fly using genetics- enhanced sterile insect technique. BMC Biology, vol. 10, No. 51 (June 2012).

Atkinson, Michael P., and others. Analyzing the control of mosquito-borne diseases by a dominant lethal genetic system. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, No. 22 (May 2007), pp. 9540–9545.

Boete, Christophe, and R. Guy Reeves. Alternative vector control methods to manage the Zika virus outbreak: more haste, less speed. *The Lancet Global Health*, vol. 4, No. 6, (June 2016).

Carvalho, Danilo, and others. Suppression of a field population of Aedes aegypti in Brazil by sustained release of transgenic male mosquitoes. *PLoS Neglected Tropical Diseases*, vol. 9, (July 2015).

Champer, Jackson, and others. Suppression gene drive in continuous space can result in unstable persistence of both drive and wild-type alleles. *Molecular Ecology*, (6 January 2021).

Crawford, Jacob E., and others. Efficient production of male Wolbachia-infected Aedes aegypti mosquitoes enables large-scale suppression of wild mosquitoes. *Nature Biotechnology*, vol. 38, No. 4 (6 April 2020), pp. 482–492.

Davis, Stephen, and others. Engineered underdominance allows efficient and economical introgression of traits into pest populations. *Journal of Theoretical Biology*, vol. 212, No. 1 (September 2001), pp. 83–98.

De Campos, André Sica, and others. Responsible Innovation and political accountability: genetically modified mosquitoes in Brazil. *Journal of Responsible Innovation*, vol. 4, No. 1 (May 2017), pp. 5–23.

De Raymond, Antoine Bernard, and Frédéric Goulet. Special Issue: Science, Technology and Food Security. Technology in Global Agriculture. *Science, Technology and Society*, vol. 25, No. 1 (March 2020), pp. 124–141.

Environmental Protection Agency. *New active ingredient for OXITEC OX5034 Aedes aegypti mosquitoes*. available at https://www.regulations.gov/docket/EPA-HQ-OPP-2019-0274. [Accessed 12 December 2023].

_____ *Response to Comments OX5034 to the Notice of Receipt of an Application for an Experimental Use Permit Number 93167-EUP-E.* 1 May 2020. Available at https://www.regulations.gov/document/EPA-HQ-OPP-2019-0274-0355.

ETC Group. *Target malaria's gene drive project fails to inform local communities of risks: New film*. 19 December 2019. Available at https://www.etcgroup.org/content/target-malarias-gene-drive-project-fails-inform-local-communities-risks-new-film.

Evans, Benjamin R., and others. Transgenic *Aedes aegypti* Mosquitoes Transfer Genes into a Natural Population. *Scientific Reports*, vol. 9, No.13047 (September 2019).

Galizi, Roberto and others. A synthetic sex ratio distortion system for the control of the human malaria mosquito. *Nature Communications*, vol. 5, No. 3977 (10 June 2014).

Gendron, William, and others. Cost-effectiveness of Precision Guided SIT for Control of Anopheles gambiae in the Upper River Region, The Gambia. *bioRxiv*, (July 2023).

GeneWatch. GeneWatch UK comments on docket identification (ID) number EPA-HQ-OPP-2019-0274-0001: New Active ingredient for Oxitec OX5034 Aedes aegypti mosquitoes. October 2019, available at http://www.genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/GeneWatch_EPA_Oxitec_consul19_fin.pdf.

_____. GeneWatch UK response to the EPA's consultation on an application 93167-EUP-2 from Oxitec (Docket No. EPA-HQ-OPP-2019-0274). September 2021, available at http://genewatch.org/uploads/f03c6d66a9b354535738483c1c3d49e4/genewatch-uk-response-to-the-epa.pdf.

Gould, Fred, and others. A Killer–Rescue system for self-limiting gene drive of anti-pathogen constructs. *Proceedings of the Royal Society B. Biological Sciences*, vol. 275, No. 1653 (December 2008), pp. 2823–2829.

Guichard, Annabel, and others. Efficient allelic drive in Drosophila. *Nature Communications*, vol. 10, No. 1640 (9 April 2019).

Harris, Angela F., and others. Successful suppression of a field mosquito population by sustained release of engineered male mosquitoes. *Nature Biotechnology,* vol. 30 (September 2012), pp. 828–830.

Harris, Angela F., and others. Field performance of engineered male mosquitoes. *Nature Biotechnology*, vol. 29 (October 2011), pp. 1034–1037.

James, Stephanie, and others. 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. *The American Journal of Tropical Medicine and Hygiene*, vol. 98, No. 6 (June 2018), pp. 1–49.

Kandul, Nikolay P., and others. Transforming insect population control with precision guided sterile males with demonstration in flies. *Nature communications*, vol. 10, No. 84 (8 January 2019).

Kandul, Nikolay P., and others. Assessment of a Split Homing Based Gene Drive for Efficient Knockout of Multiple Genes. *G3 Genes Genomes Genetics*, vol. 10, No. 2 (1 February 2020), pp. 827–837.

Kandul, Nikolay P., and others. Precision guided Sterile males suppress populations of an invasive crop pest. *GEN Biotechnology*, vol. 1, No. 4 (18 August 2022), pp. 372–385.

Kandul, Nikolay P., and others. Temperature-inducible precision-guided sterile insect technique. *The CRISPR Journal*, vol. 4, No. 6 (3 November 2021), pp. 822–835.

Kapranas, Apostolos, and others. Review of the role of sterile insect technique within biologically- based pest control–An appraisal of existing regulatory frameworks. *Entomologia Experimentalis et Applicata*, vol. 170, No. 5 (February 2022), pp. 385–393.

Koenraadt, Constantianus J.M., and others. *Innovative strategies for vector control*, vol. 6. Wageningen Academic Publishers, Wageningen, 2021.

Li, Ming, and others. Targeting sex determination to suppress mosquito populations. *bioRxiv*, (20 April 2023).

Li, Ming, and others. Suppressing mosquito populations with precision guided sterile males. *Nature Communications*, vol. 12, No. 5374 (10 September 2021).

Liu, Xinsheng, and others. General science- technology orientation, specific benefit–risk assessment frame, and public acceptance of gene drive biotechnology. Risk Analysis (26 October 2023).

Lowe, Ronald E., and others. Efficiency of techniques for the mass release of sterile male *Anopheles albimanus Wiedemann in* El Salvador. *The American Journal of Tropical Medicine*, vol. 29 No. 4 (July 2018), pp. 695–703.

Mains, James W., and others. Female adult Aedes albopictus suppression by Wolbachia-infected male mosquitoes. *Scientific Reports*, vol. 6, No. 33846 (23 September 2016).

Marshall, John M., and Omar S. Akbari. Can CRISPR-based gene drive be confined in the wild? a question for molecular and population biology. *ACS Chemical Biology*, vol. 13, No. 2 (25 January 2018), pp. 424–430.

Marshall, John M., and Valeri N. Vásquez. Field trials of gene drive mosquitoes: Lessons from releases of genetically sterile males and Wolbachia-infected mosquitoes. in Genetically Modified and other Innovative Vector Control Technologies: Eco-bio-social Considerations for Safe Application. Springer, Singapore, January 2022.

Meccariello, Angela, and others. Engineered sex ratio distortion by X-shredding in the global agricultural pest Ceratitis capitata. *BMC Biology*, vol. 19, No. 78 (16 April 2021).

Noble, Charleston, and others. Daisy-chain gene drives for the alteration of local populations. *Proceedings of the National Academy of Science United States*, vol. 116, No. 17 (July 2018), pp. 8275–8282.

Oberhofer, Georg, and others. Split versions of Cleave and Rescue selfish genetic elements for measured self limiting gene drive. *PLOS Genetics*, vol. 17, No. 2 (18 February 2021).

Pham, Thai Binh, and others. Experimental population modification of the malaria vector mosquito, Anopheles stephensi. *PLOS Genetics*, vol. 15, No. 12 (19 December 2019).

Raban, Robyn and others. Manipulating the destiny of wild populations using CRISPR. *Annual Review of Genetics*, vol. 57 (November 2023), pp. 361–390.

Reavey, Catherine E., and others. Self-limiting fall armyworm: a new approach in development for sustainable crop protection and resistance management. *BMC Biotechnology*, vol. 22, No. 5 (January 2022).

Rode, Nicolas O. Self-limiting drives have been suggested to potentially spread indefinitely under the right ecological conditions. *G3 Genes Genomes Genetics*, vol. 10, No. 9 (1 September 2020), pp. 3403–3415.

Schwindenhammer, Sandra. The Rise, Regulation and Risks of Genetically Modified Insect Technology in Global Agriculture. *Sage Journals*, vol. 24, No. 1 (January 2020).

Shelton, Anthony M., and others. First field release of a genetically engineered, self-limiting agricultural pest insect: evaluating its potential for future crop protection. *Frontiers Bioengineering and Biotechnology*, vol. 7 No. 482 (January 2020).

Sirinathsinghji, Eva, Third World Network. *Bt crops past their sell-by date: A failing technology searching for new markets?* Penang, 2022. Available at https://www.twn.my/title2/biosafety/pdf/bio19.pdf.

Smidler, Andrea L., and others. Eliminating malaria vectors with precision guided sterile males. *bioRxiv* (July 2023).

Target Malaria. Target Malaria proceeded with a small-scale release of genetically modified sterile male mosquitoes in Bana, a village in Burkina Faso. 1 July 2019.

Terradas, Gerard, and others. Inherently confinable split-drive systems in Drosophila. *Nature Communications*, vol. 12, No. 1480 (5 March 2021).

Then, Christoph, and others. Spatio-temporal controllability and environmental risk assessment of genetically engineered gene drive organisms from the perspective of EU GMO Regulation. *Integrated Environmental Assessment and Management*, vol. 16, No. 5 (April 2020), pp. 555–568.

Thomas, Dean D., and others. Insect population control using a dominant, repressible, lethal genetic system. *Science*, vol. 287, No. 5462 (31 March 2000).

Verkuijl, Sebald A. N., and others. A CRISPR endonuclease gene drive reveals two distinct mechanisms of inheritance bias. *bioRxiv*, (December 2020).

Waltz, Emily. First genetically modified mosquitoes released in the United States. *Nature*, vol. 593, No. 7858 (May 2021), pp. 175–176.

Windbichler, Nikolai, and others. Targeting the X chromosome during spermatogenesis induces Y chromosome transmission ratio distortion and early dominant embryo lethality in Anopheles gambiae. *PLoS Genetics*, vol. 4, No. 12 (5 December 2008).

World Health Organization. *Seventh meeting of the vector control advisory group (VCAG).* Geneva, October 2017. Available at https://iris.who.int/bitstream/handle/10665/259743/WHO-HTM-NTD-VEM-2017.11-eng.pdf?sequence=1.

Zheng, Xiaoying, and others. Incompatible and sterile insect techniques combined eliminate mosquitoes. Nature, vol. 572 (July 2019), pp. 56–61.

D. Integration of artificial intelligence and machine learning

Abraham Stern. NVIDIA expands large language models to biology. NVIDIA, blog, 20 September 2022.

Adler, Aaron. May 2022 CACM: Artificial Intelligence for Synthetic Biology. Association for Computing Machinery, YouTube video, 26 April 2022.

Batzoglou, Serafim. Large Language Models in Molecular Biology: Deciphering the language of biology, from DNA to cells to human health. Medium, 2 June 2023

Booker, Robin. The secret messages of plants. The Western Producer, 29 December 2022.

Dan Miller. Deere Works to Use Its Camera Technologies to Read Stress Markers in Plants. Progressive Farmer, 17 January 2023.

De Souza, Mervyn. Developing A More Scalable Enzymatic Process for Allulose with Ambrosia Bio. Ginkgo Bioworks. [Accessed 11 December 2023].

Engineering Biology Research Consortium. An Assessment of Short-Term Milestones in EBRC'sRoadmap, Engineering Biology. March 2023.

_____. Engineering Biology for Climate & Sustainability: A Research Roadmap for a Cleaner Future. [Accessed 11 December 2023].

Eslami, Mohammed, and others. Artificial intelligence for synthetic biology. *Communications of the ACM*, vol. 65, No. 6 (April 2022), pp. 88–97.

Farmer, Harry. DNA.I.: Early findings and emerging questions on the use of AI in genomics. Ada Lovelace Institute, report, 31 August 2023.

Ginkgo Bioworks. Ginkgo Bioworks and Google Cloud Partner to Build Next Generation AI Platform for Biological Engineering and Biosecurity. 29 August 2023.

Gupta, Geetika. Speaking the Language of the Genome: Gordon Bell Winner Applies Large Language Models to Predict New COVID Variants. NVIDIA, 17 November 2022.

Hassoun, Soha, and others. Artificial Intelligence for Biology. *Integrative and Comparative Biology*, vol. 61, No. 6 (December 2021), pp. 2267–2275.

Howes, Laura. Generative AI is dreaming up new proteins. *C & en chemical and engineering news,* vol. 101, No. 12 (April 2023).

iGEM Foundation. Jason Kelly & Oliver Morton Fireside Chat. Podcast, YouTube, episode 34. Available at https://www.youtube.com/watch?v=snt-fMsCDVI).

Jansson, Janet K. Microorganisms, climate change, and the Sustainable Development Goals: progress and challenges. *Nat Rev Microbiology*, vol. 21, No. 10 (October 2023), pp. 622–623.

Johnson, Charlie D., and others. Engineering Biology Research Consortium. *Security Considerations at the Intersection of Engineering Biology and Artificial Intelligence*. Engineering Biology Research Consortium, Report, Emeryville, California, 2023.

Ledford, Heidi. Neurons in a dish learn to play Pong – what's next? *Nature*, 12 October 2022.

Lin, Zeming, and others. Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science*, vol. 379, No. 6637 (16 March 2023), pp. 1123–1130.

Liu, Schengchao, and others. A Text-guided Protein Design Framework. *arXiv*, vol. 2 (December 2023).

Lu, Hongyuan, and others. Machine learning-aided engineering of hydrolases for PET depolymerization. *Nature*, vol. 604 (April 2022), pp. 662–667.

Mok, Kimberley. Distributed E. Coli Biocomputer Solves Maze Problems. The news stack, 19 November 2021.

Naiduand, Ravi, and others. Chemical pollution: A growing peril and potential catastrophic risk to humanity. Environment International, vol. 156 (November 2021).

Nayarisseri, Anuraj, and others. Artificial Intelligence, Big Data and Machine Learning Approaches in Precision Medicine & Drug Discovery. *Bentham Science*, vol. 22, No. 6 (January 2021), pp. 631–655.

Nissinoff, Doug. Revolutionizing Small Molecule Manufacturing with the AI/ML Paradigm Shift: Producing the 'Golden Batch'. LinkedIn, 17 August 2023.

Radivojević, Tijana, and others. A machine learning Automated Recommendation Tool for synthetic biology. *Nature Communications*, vol. 11, No. 4879 (September 2020).

Roberts, Siobhan. An E. coli biocomputer solves a maze by sharing the work. MIT Technology Review, 9 November 2021.

Rojo, Fernando Perez, and others. Microbial synthetic biology for plant metabolite production: a strategy to reconcile human health with the realization of the UN Sustainable Development Goals. *Biofuels, Bioproducts and Biorefining*, vol. 7, No. 6 (July 2023), pp. 1485–1495.

Shapiro, Scott. The Coming Wave by Mustafa Suleyman review – a tech tsunami. the Guardian, 8 September 2022.

The ai podcast. Anima Anandkumar on Using Generative AI to Tackle Global Challenges - Ep. 203. SoundCloud, podcast, September 2023.

University of California. AI technology generates original proteins from scratch: Natural language model jumpstarts protein design with creation of active enzymes. 26 January 2023.

Wiggers, Kyle. Stability AI backs effort to bring machine learning to biomed. TechCrunch, 4 November 2022.

Yang, Dongsoo, and others. Systems metabolic engineering as an enabling technology in accomplishing sustainable development goals. *Microbial Biotechnology*, vol. 10, No. 5 (September 2017), pp. 1254–1258.

E. Inequity in the participation of developing countries in the context of synthetic biology

Abberton, Michael, and others. Global agricultural intensification during climate change: a role for genomics. *Plant biotechnology*, vol. 14, No. 4 (April 2016), pp. 1095–1098.

Australia's National Science Agency. A National Synthetic Biology Roadmap: Identifying commercial and economic opportunities for Australia. CSIRO, 2021

Beall, Anne E., and Robert M. Friedman. "Biotechnology by Mid-Century: Assessing current capabilities, anticipating tomorrow's leaders, A 12-country comparison". Summary Report, Craig Venter Institute, 30 June 2020.

Bender, S. Franz, and others. An Underground Revolution: Biodiversity and Soil Ecological Engineering for Agricultural Sustainability. *Trends in ecology and evolution,* vol. 31, No. 6 (June 2016), pp. 440–452.

Borel, Brooke. CRISPR, microbes and more are joining the war against crop killers. *Nature*, vol. 543, No. 7645 (March 2017).

Bourzac, Katherine. Bioengineering: Solar upgrade. *Nature*, vol. 544, No. 7651 (April 2017).

De Steur, Hans, and others. GM biofortified crops: potential effects on targeting the micronutrient intake gap in human populations. *Current opinion in Biotechnology*, vol. 44 (April 2017), pp. 181-188.

Diaz, S. Global assessment report on biodiversity and ecosystem services of the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. *Science and Policy for People and Nature*, (November 2019).

French, K.E. Harnessing synthetic biology for sustainable development. *Nature*, vol. 2, No. 4 (April 2019), pp. 250–252.

Gobierno del Ecuador. Reglamento al Régimen Común Sobre Acceso a los Recursos Genéticos. Decreto Ejecutivo 905. 2011.

Intriago-Barreno, Richard, and Elizabeth Bravo-Velásquez. E. Primera detección de Soya transgénica (Glycinemax) cultivada en la Costa ecuatoriana usando métodos de monitoreo participativo. *Cienciamérica*, vol. 5, No. 1 (2017), pp. 75–82.

Lyal, Chris H.C. Digital Sequence Information on Genetic Resources and the Convention on Biological Diversity. in *Global Transformations in the Use of Biodiversity for Research and Development*, (February 2022), pp. 589–619

Macfarlane, Nicholas B.W., and others. Direct and indirect impacts of synthetic biology on biodiversity conservation. *iScience,* vol. 25, No. 11 (20 October 2022).

Moreno-Mateos, David, and others. Anthropogenic ecosystem disturbance and the recovery debt. *Nature Communications,* vol. 8, No. 14163 (January 2017).

Nathaniel, Solomon P., and others. Natural resource, globalization, urbanization, human capital, and environmental degradation in Latin American and Caribbean countries. *Environmental Science and Pollution Research*, vol. 28, (February 2021), pp. 6207–6221.

Precedence Research. Synthetic Biology Market. Available at https://www.precedenceresearch.com/synthetic-biology-market.

United Nations Conference on Trade and Development. *Synthetic Biology and its Potential Implications for Biotrade and Access and Benefit-Sharing.* 2019.

Winkler, Karina, and others. Global land use changes are four times greater than previously estimated. *Nature communications*, vol. 12, No. 2501 (May 2021).

II. Additional trends and issues in synthetic biology prioritized by the multidisciplinary Expert Group

A. Use of synthetic biology in wild organisms in the context of resilience in threatened species

Bui, Michelle, and others. CRISPR mediated transactivation in the human disease vector Aedes aegypti. *PLoS Pathogens*, vol. 19, No. 1 (January 2023).

Chakravarti, Leela J., and others. Rapid thermal adaptation in photosymbionts of reef- building corals. *Global Change Biology,* vol. 23, No. 11 (November 2017), pp. 4675–4688.

Cleves, Phillip A. A Need for Reverse Genetics to Study Coral Biology and Inform Conservation Efforts. *in Coral Reef Conservation and Restoration in the Omics Age*, vol. 15, Aranda Lastra, M., eds. Springer, Cham, 2022.

Cleves, Phillip A., and others. Reduced thermal tolerance in a coral carrying CRISPR-induced mutations in the gene for a heat-shock transcription factor. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 117, No. 46 (November 2020), pp. 28899–28905.

Coleman, Melinda A., Hugh D. Goold. Harnessing synthetic biology for kelp forest conservation. *Journal of Phycology*, vol. 55, No. 4 (August 2019), pp. 745–751.

Connolly, John B. and others. 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. *Malaria Journal,* vol. 20, No. 170 (March 2021), pp. 170.

Cottingham, Ellen Peterson. "Construction of feline alphaherpesvirus 1 derived immunocontraceptives for the population management of feral and domestic cats in Australia", PhD thesis, Veterinary and Agricultural Sciences Collected Works, University of Melbourne, 2022.

Ebeling, Smillo, and Ulrich Gebhard. Ideas, hopes, and fears: what young adults think about genome editing, nature, and society. *Cultural Studies of Science Education*, vol. 17 (2022), pp. 745–764.

Esha, Shah, and others. The complexity of the gene and the precision of CRISPR: What is the gene that is being edited? *Elementa: Science of the Anthropocene*, vol. 9, No. 1 (October 26, 2021).

Frieß, Johannes, and others. Umbruch in der Biotechnologie: Sprung aus dem Labor in die Natur. *Natur und Landschaft*, vol. 95, No. 5 (May 2020), pp. 209–214.

Germany, Federal Agency for Nature Conservation. *Genetic engineering, nature conservation and*

Biological diversity: Boundaries of design. Viewpoint, 24 October 2022.

Gierus, Luke, and others. Leveraging a natural murine meiotic drive to suppress invasive populations. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 119, No. 46 (November 2022).

Giese, Bernd. The viral era: New biotechnologies give humans an unprecedented control over Nature and require appropriate safeguards. *EMBO Reports*, vol. 22, No. 9 (September 2021).

Hughes, Terry P., and others. Spatial and temporal patterns of mass bleaching of corals in the Anthropocene. *Science,* vol. 359, No. 6371 (January 2018), pp. 80–83.

International Union for Conservation of Nature, Kent H. Redford and others. *Genetic frontiers for conservation.* Switzerland 2019.

John Godwin, and others. Rodent gene drives for conservation: opportunities and data needs. *Royal Society Publishing*, vol. 286, No. 1914 (November 2019).

Karageorgi, Marianthi, and others. Genome editing retraces the evolution of toxin resistance in the monarch butterfly. *Nature*, vol. 574, No. 409 (October 2019).

Kayal, Mohsen, and others. Predator crown-of-thorns starfish (Acanthaster planci) outbreak, mass mortality of corals, and cascading effects on reef fish and benthic communities. *PloS One*, vol. 7, No. 10 (October 2012*).*

Kohl, P.A., and others. Public views about editing genes in wildlife for conservation. *Conservation Biology*, vol. 33, No. 1286 (December 2019), pp.745–764.

Koplin, Julian J., Christopher Gyngell, and Julian Savulescu. Germline gene editing and the precautionary principle. *Bioethics*, vol. 34, No. 12609 (June 2019), pp. 49–59.

Kosch, Tiffany A., and others. Genetic approaches for increasing fitness in endangered species. *Trends in Ecology & Evolution*, vol. 37, No. 4 (April 2022), pp. 332–345.

Lord, Errol. What you're rationally required to do and what you ought to do (are the same thing!). *Mind,* vol. 126, No. 504 (January 2017), pp. 1109–1154.

Macfarlane, Nicholas B.W. and others. Direct and indirect impacts of synthetic biology on biodiversity conservation. *iScience*, vol. 25, No. 11 (November 2022).

Mankad, Aditi and others. Genetically Engineering Coral for Conservation: Psychological Correlates of Public Acceptability. *Frontiers in Marine Science*, vol. 8 (November 2021).

McLaren, Duncan and others. The co-evolution of technological promises, modelling, policies and climate change targets. *Nature Climate Change*, vol. 10 (April 2020), pp. 392–397.

Newhouse, Andrew E. and William A. Powell. Intentional introgression of a blight tolerance transgene to rescue the remnant population of American chestnut. *Conservation Science and Practice*, vol. 5, No. 12 (December 2023.

Pearson, Dean E., and others. Evaluating unintended consequences of intentional species introductions and eradications for improved conservation management. *Conservation Biology*, vol. 35, No. 1 (March 2021).

Piaggo, Antoinette J., and others. Is It Time for Synthetic Biodiversity Conservation? *trends in Ecology and evolution,* vol. 31, No. 2 (February 2017), pp. 97–107.

Popkin, Gabriel. For the First Time, Genetically Modified Trees Have Been Planted in a U.S. Forest. New York Times, 16 February 2023.

Powell, William A., and others. Developing Blight-Tolerant American Chestnut Trees. *Cold spring harbor perspectives in biology*, vol. 1, (2021).

Reynolds, Jesse L., and others. Engineering biological diversity: the international governance of synthetic biology, gene drives, and de-extinction for conservation. *Current Opinion in Environmental Sustainability*, vol. 49 (April 2021), pp. 1–6.

Ricciardi, Anthony, and others. Four priority areas to advance invasion science in the face of rapid environmental change. *Canadian Science Publishing*, vol. 29, No. 2 (June 2021), pp. 119–141.

Samuel, Michael D., and others. Facilitated adaptation for conservation – Can gene editing save Hawaii's endangered birds from climate driven avian malaria? *Biological Conservation*, vol. 241, (January 2020).

Sandler, Ronald, and others. The ethics of genetic engineering and gene drives in conservation. *Conservation Biology*, vol. 34, No. 2 (September 2021), pp. 378–385.

Sandler, Ronald, and others. The ethics of reviving long extinct species. *Conservation Biology*, vol. 28, No. 2 (April 2014), pp. 354–360.

Sandler, Ronald. Should we engineer species in order to save them? *Environmental Ethics*, vol. 41, No. 3 (2019), pp. 221–236.

United Nations, Treaty Series, vol. 2226, No. 30619.

Simard, Suzanne W. Mycorrhizal Networks Facilitate Tree Communication, Learning, and Memory. *In Memory and Learning in Plants*, (April 2018), pp. 191–213.

Simmons, Benno I., and others. Estimating the risk of species interaction loss in mutualistic communities. *PLOS Biology*, vol. 18, No. 8 (August 2020).

Simonis, George.*Konzepte und Verfahren der Technikfolgenabschätzung*. Springer VS Wiesbaden, Germany, 2013.

Snow. A, and others. Genetically Engineered Organisms and the Environment: Current Status and Recommendations. *Ecological Applications*, vol. 15, No. 2 (April 2005), pp. 377–404.

Tiedje, James M., and others. The Planned Introduction of Genetically Engineered Organisms: Ecological Considerations and Recommendations. *Ecology*, vol. 70, No. 2 (April 1989), pp. 298–315.

Tim Harvey-Samuel, and others. *Culex quinquefasciatus*: status as a threat to island avifauna and options for genetic control. *CABI Agriculture and Bioscience*, vol. 2, No. 9 (March 2021).

Unai, Pasqual, and others. Summary for Policymakers of the Methodological Assessment of the Diverse Values and Valuation of Nature. *Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services*, vol. 1.2 (July 2022).

Warburton, Bruce, and others. Alternatives for mammal pest control in New Zealand in the context of concerns about 1080 toxicant (sodium fluoroacetate). *New Zealand Journal of Zoology*, vol. 49, No. 2 (October 2021), pp. 79–121.

World Conservation Congress Marseille. 075 - Towards development of an IUCN policy on synthetic biology in relation to nature conservation. 30 September 2021.

B. Synthetic biology applications for bioremediation, biodegradation or biomining

Abo-Alkasem, Mohamed I., and others. Microbial bioremediation as a tool for the removal of heavy metals. Bulletin of the National Research Centre, vol. 47, No. 31 (February 2023).

C. Microbiome engineering for non-medical purposes

Arkea Bio. Available at https://www.arkeabio.com [Accessed 11 December 2023].

Bolt Threads. Bolt Technology–Meet Microsilk. [Accessed 8 December 2023].

Business Wire. Murdock, Andy. The Audacious Project to Support a New Frontier for CRISPR: Editing Microbiomes to Tackle Climate Change and Chronic Disease. 17 April 2023.

Carbonell, Pablo, and others. An automated Design-Build-Test-Learn pipeline for enhanced microbial production of fine chemicals. *Biology*, vol. 1, No. 66 (June 2018).

Chen, Jian, and others. A survey of drug resistance *bla* genes originating from synthetic plasmid vectors in six Chinese rivers. *Environmental science & technology*, vol. 46, No. 24 (December 2012), pp. 13448–13454.

D'aes, Jolien, and others. Metagenomic Characterization of Multiple Genetically Modified *Bacillus* Contaminations in Commercial Microbial Fermentation Products. *Life*, vol. 12, No. 1971 (November 2022).

De Schutter, Kristof, and others. RNAi-Based Biocontrol Products: Market Status, Regulatory Aspects, and Risk Assessment. *Frontiers in Insect Science*, vol. *1* (January 2022).
Deckers, Marie, and others. First monitoring for unauthorized genetically modified bacteria in food enzymes from the food market. *Food Control*, vol. 135, No. 108665 (May 2022).

Folium Science. Available at https://foliumscience.com/.[Accessed 11 December 2023].

Genetic Engineering and Biotechnology News. IGI wins $70 million to study microbiome engineering for health, Climate Challenges. 20 April 2023. Available at https://www.genengnews.com/insights/igi-wins-70-million-to-study-microbiome-engineering-for-health-climate-challenges/.

Ginkgo Bioworks. Ginkgo completes acquisition of Zymergen. 19 October 2022.

Gong, Fuyu, Zhen Cai, and Yin Li. Synthetic biology for CO2 fixation. *Science China Life Sciences*, vol. 59, (October 2016), pp. 1106–1114.

Hehemann, Jan- Hendrick, and others. Bacteria of the human gut microbiome catabolize red seaweed glycans with carbohydrate-active enzyme updates from extrinsic microbes. *Proceedings of the National Academy of Sciences of the United States of America*, vol. 109, No. 48 (October 2012), pp. 19786–19791.

Heinemann, Jack A., and others. Differentiated impacts of human interventions on nature: Scaling the conversation on regulation of gene technologies. *Elementa Science of the Anthropocene*, vol. 9, No. 1 (March 2017).

Jagadevan, Sheeja, and others. Recent developments in synthetic biology and metabolic engineering in microalgae towards biofuel production. *Biotechnology Biofuels and Bioproducts*, vol. 11, No. 185 (June 2018).

King, Samuel J., and others. Synthetic biology for improved hydrogen production in *Chlamydomonas reinhardtii*. *Microbial Biotechnology*, *Applied Microbiology International*, vol. 15, No. 7 (March 2022), pp. 1946–1965.

Leonard, Sean P., and others. Engineered symbionts activate honeybee immunity and limit pathogens. *Science*, vol. 367, No. 6477 (January 2020), pp. 573–576.

Liu, Zihe, Junyang Wang, and Jens Nielsen. Yeast synthetic biology advances biofuel production. *Current Opinion in Microbiology*, vol. 65, (October 2021), pp. 33–39.

Murdock, Andy. IGI's 'Audacious' new frontier for CRISPR: Editing Microbiomes for Climate and Health. Innovative Genomics Institute, 17 April 2023.

Novamont. The development of innovative industrial biotechnology processes complete our integrated biorefineries in local area. A versalis Company, 2021.

Paxton, Robert J. A microbiome silver bullet for honey bees. *Science*, vol. 367, No. 6477 (January 2020), pp. 504–506.

Rubin, Benjamin E., and others. Species- and site-specific genome editing in complex bacterial communities. *Nature Microbiology*, vol. 7, No. 1 (December 2021), pp. 34–47.

Ryu, Min-Hyung, and others. Control of nitrogen fixation in bacteria that associate with cereals. *Nature Microbiology*, vo. 5, No. 2 (December 2019), pp. 314–330.

Scharfenstein, Hugo J., and others. Chemical mutagenesis and thermal selection of coral photosymbionts induce adaptation to heat stress with trait trade-offs. *Evolutionary Applications*, vol. 16, No. 9 (September 2023), pp. 1549–1567.

Voigt, Christopher A. Synthetic biology 2020–2030: six commercially-available products that are changing our world. *Nature Communications*, vol. 11, No.6379 (December 2020).

D. Engineered bacteria for nitrogen-fixation and fertilizers

Gao, Yunhu, and André Cabrera Serrenho. Greenhouse gas emissions from nitrogen fertilizers

could be reduced by up to one-fifth of current levels by 2050 with combined interventions. *Nature Food*, vol. 4, No. 2 (February 2023), pp. 170–178.

Voigt, Christopher A. Synthetic biology 2020–2030: six commercially-available products that are

changing our world. *Nature Communications*, vol. *11, No.* 1 (December 2020), pp. 10–15.

Wen, Amy, and others. Enabling biological nitrogen fixation for cereal crops in fertilized fields. ACS Synthetic Biology, vol. 10, No. 12 (December 2021), pp. 3264–3277.

E. Genome-edited plants

Agapito-Tenfen, Sarah Z., and others. Revisiting Risk Governance of GM Plants: The Need to Consider New and Emerging Gene-Editing Techniques. *Frontiers in Plant Science* 9, vol. 9, No. 1874 (December 2018).

Ahmed, Akter U., and others. *Impacts of BT Brinjal (eggplant) technology in Bangladesh*. International Food Policy Research Institute, Bangladesh Policy Research and Strategy Support Program. 2019. Available at https://pdf.usaid.gov/pdf_docs/PA00TZ7Z.pdf.

Alo-Kokko, Kristina, and others. Economic and ecosystem impacts of GM maize in South Africa. *Global Food Security*, vol. 29, No. 100544 (June 2021).

Anderson, Emily M., and others. Systematic analysis of CRISPR-Cas9 mismatch tolerance reveals low levels of off-target activity. *J Biotechnology*, vol. 211 (October 2015), pp. 56–65.

Ayub, Nicolas and Gabriel Soto. Multiple challenges in the development of commercial crops using CRISPR/Cas technology. *Plant Science*, vol. 335, No.111809 (October 2023).

Bjørn, and others. Non-safety Assessments of Genome-Edited Organisms: Should They be Included in Regulation? *Science and Engineering Ethics*, vol. 26, No. 5 (May 2020), pp. 2601–2627.

Braatz, Janina, and others. CRISPR-Cas9 Targeted Mutagenesis Leads to Simultaneous Modification of Different Homoeologous Gene Copies in Polyploid Oilseed Rape (*Brassica napus*). *Plant Physiology*, vol. 174, No. 2 (June 2017), pp. 935–942**.**

Brookes, Graham, and Peter Barfoot. Environmental impacts of genetically modified (GM) crop use 1996-2018: impacts on pesticide use and carbon emissions. *GM Crops & Food*, vol. 11, No. 4 (July 2020), pp. 215–241.

Brookes, Graham. Farm income and production impacts from the use of genetically modified (GMO) crop technology. *GM Crops & Food,* vol. 13, No.1 (July 2022), pp.171–195.

Business Wire. First Commercial Sale of Calyxt High Oleic Soybean Oil on the U.S. Market. 26 February 2019.

Cho, Seung Woo. Analysis of off-target effects of CRISPR/Cas-derived RNA-guided endonucleases and nickases. *Genome Res,* vol. 24, No. 1 (January 2015), pp. 132–141.

Council of the European Union. *Commission staff working document impact Assessment report*. Brussels, 2023.

_____. *Proposal for a regulation of the European parliament and of the council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625*. Brussels, 2023.

_____. *Study on the status of new genomic techniques under Union law and in light of the ruling case C-528/16*. Brussels, 2021.

Cover Cress. An emerging seed technology. [Accessed 15 December 2023].

CropLife International, AgbioInvestor. *Time and Cost to Develop a New GM Trait.* Final report, May 2022. Available at https://croplife.org/wp-content/uploads/2022/05/AgbioInvestor-Trait-RD-Branded-Report-Final-20220512.pdf.

CropLife International. Database of the safety and benefits of biotechnology. Available at https://biotechbenefits.croplife.org/. [Accessed 15 December 2023].

Eckerstorfer, Michael F., and others. An EU perspective on biosafety considerations for plants developed by genome editing and other new genetic modification techniques (nGMs). *Frontiers in Biotechnology*, vol. 7, No. 31 (March 2019).

Eckerstorfer, Michael F., and others. Biosafety of Genome Editing Applications in Plant Breeding: Considerations for a Focused Case-Specific Risk Assessment in the EU. *Biotech,* vol. 10, No. 10 (June 2021).

Entine, Jon, and others. Regulatory approaches for genome edited agricultural plants in select countries and jurisdictions around the world. *Transgenic Research*, vol. 30, No. 4 (May 2021), pp. 551–584.

European Food Safety Authority, Panel on Genetically Modified Organisms. Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function. *EFSA journal*, vol. 10, No. 2943 (October 2012).

European Comission, Broothaerts, Wim, and others. *Detection of food and feed plant products obtained by targeted mutagenesis and cisgenesis*, EUR 31521 EN. Publications Office of the European Union, Luxembourg, 2023.

European Commission, Directorate-General for Research and Innovation. *European Group on Ethics in Science and New Technologies opinion on the Ethics of Genome Editing*. Publications Office, 2021. Available at https://data.europa.eu/doi/10.2777/659034.

European Commission, Parisi, Claudia, and Emilio Rodríguez-Cerez. *Current and future market applications of new genomic techniques*. Luxembourg, 2021.

European Network of Scientists for Social and Environmental Responsibility. ENSSER Statement: New genetic modification techniques and their products pose risks that need to be assessed. 8 November 2019. Available at https://ensser.org/publications/2019-publications/ensser-statement-new-genetic-modification-techniques-and-their-products-pose-risks-that-need-to-be-assessed/.

European Network of Scientists for social and Environmental Responsibility. Scientific critique of Leopoldina and EASAC statements on genome edited plants in the EU: Press Release: A distortion

of science and a danger to public and environmental safety", 26 April 2021. Available at https://ensser.org/wp-content/uploads/2021/04/Greens-EFA-GMO-Study- 1.pdf.

Eusage, European Sustainable Agriculture Through Genome Editing. EU-SAGE Welcomes the European Commission's Regulatory Proposal for Plants Obtained by Certain New Genomic Techniques and Their Food and Feed. 6 July 2023.

Food and Agriculture Organization of the United Nations. "The State of Food Security and Nutrition in the World 2023 - Urbanization, agrifood systems transformation and healthy diets across the rural–urban continuum". 2023. Available at https://www.fao.org/3/cc3017en/cc3017en.pdf.

France, Minister of Agriculture, Agri-Food and Forestry. *Deliberate release of genetically modified organisms – Directive 2001/18/EC – Article 3(1) – Point 1 of Annex I B – Scope – Exemptions – Techniques/methods of genetic modification which have conventionally been used and have a long safety record – In vitro random mutagenesis).* 25 July 2018, InfoCuria Case-Law.

Franziska Koller, and others. The need for assessment of risks arising from interactions between NGT organisms from an EU perspective. *Environmental Sciences Europe*, vol. 35, No. 27 (April 2023).

Franziska, Koller, and Michael Cieslak. A perspective from the EU: unintended genetic changes in plants caused by NGT–their relevance for a comprehensive molecular characterisation and risk assessment. *Frontiers in Bioengineering and Biotechnology*, vol. 11, No. 1276226 (October 2023).

Germany, Federal Agency for Nature Conservation. Genetic engineering, nature conservation and biological diversity. Bonn, Germany, October 2022.

_____. New developments and regulatory issues in plant genetic engineering. Bonn, Germany, October 2021.

_____. Ad Hoc expert opinion on the judgment of the European Court of Justice in Case C-688/21. Bonn, February 2023.

Graham Brookes. Genetically modified (GM) crop use 1996-2020: Environmental impacts associated with pesticide use change. *GM Crops & Food*, vol. 13, No. 1 (October 2022), pp. 262–289.

_____. Genetically modified (GM) crop use in Colombia: Farm level economic and environmental contributions. *GM Crops & Food*. vol. 11, No. 3 (February 2020), pp. 140–153.

_____. The farm level economic and environmental contributions of Intacta soybeans in South America: The first five years. GM *Crops & Food*, vol. 9, No. 3 (August 2018), pp. 140–151.

_____. Twenty-one years of using insect resistant (GM) maize in Spain and Portugal: Farm-level economic and environmental contributions. *GM Crops & Food,* vol. 10, No. 2 (May 2019), pp. 90–101.

Herman, Rod A., and others. Transparency in risk-disproportionate regulation of modern crop-breeding techniques. *GM Crops & Food*, vol. 12, No. 1 (April 2021), pp. 376–381.

Hüdig, Meike, Natalie Laibach, and Anke-Christiane Hein. Genome Editing in Crop Plant Research–Alignment of Expectations and Current Developments. *Plants*, vol. 11, No. 2 (January 2022), pp. 212.

Huwaida, Yaqoob, and others. Integrating genomics and genome editing for orphan crop improvement: A bridge between orphan crops and modern agriculture system. *GM Crops & Food.* vol. 14, No. 1 (January 2023), pp. 1–20.

Italy, G20, *10th Meeting of Agricultural Chief Scientists (MACS).* 2021.

J. G. Monroe, and others. The lowest hanging fruit: Beneficial gene knockouts in past, present and future crop evolution. *Current Plant Biology*, vol. 24, No. 100185 (December 2020).

J. Grey Monroe, and others. Mutation bias reflects natural selection in Arabidopsis thaliana. *Nature*, vol. 602, No. 1 (January 2022), pp. 101–105.

James Reed, and others. Elucidation of the pathway for biosynthesis of saponin adjuvants from the soapbark tree. *Science*, vol. 379, No. 6638 (March 2023), pp. 1252–1264.

Jenkins, Daniel, and others. Impacts of the regulatory environment for gene editing on delivering beneficial products. *In Vitro Cellular & Developmental Biology Plant,* vol. 57, No. 4 (August 2021), pp. 609–626.

Jocelyn Kaiser. Gene therapy trials for sickle cell disease halted after two patients develop cancer. Science Insider, 16 February 2021.

K. Kishimoto, and others. An effective microinjection method for genome editing of marine aquaculture fish: tiger pufferfish *Takifugu rubripes* and red sea bream *Pagrus major*. *Fisheries Science*, vol. 85, No. 1 (February 2019), pp. 217–226.

Kaiser, Natalie, and others. The role of conventional plant breeding in ensuring safe levels of naturally occurring toxins in food crops. *Trends in Food Science & Technology,* vol. 100, (June 2020), pp. 51–66.

Kalaitzandonakes, Nicholas, and others. The economics and policy of genome editing in crop improvement. *The Plant Genome*, vol. 16, (November 2022).

Karavolias, Nicholas G. Application of gene editing for climate change in agriculture. *Frontiers in Sustainable Food Systems*, vol. 6, No. 685801 (September 2021).

Karlson, Dale, and others. Targeted mutagenesis of the multicopy *Myrosinase* gene family in allotetraploid Brassica juncea reduces pungency in fresh leaves across environments. *Plants*, vol. 11, No. 2494 (September 2022).

Katharina Kawall. The Generic Risks and the Potential of SDN-1 Applications in Crop Plants. *Plants*, vol. 10, No. 11 (October 2021).

Kaur, Harmeet, and others. CRISPR/Cas0-mediated genome editing is revolutionising the improvement of horticultural crops: Recent advances and future prospects. *Scientia Horticulturae,* vol. 289, No. 110476 (November 2021).

Kawall, Katharina, and others. Broadening the GMO risk assessment in the EU for genome editing technologies in agriculture. *Environmental Sciences Europe*, vol. 32, No. 106 (August 2020).

Kawall, Katharina, and others. New Possibilities on the Horizon: Genome Editing Makes the Whole Genome Accessible for Changes. *Frontiers in Plant Science*, vol. 10, No. 525 (April 2019).

Kawall, Katharina. Genome-edited Camelina sativa with a unique fatty acid content and its potential impact on ecosystems. *Environmental Sciences Europe*, vol. 33, No. 38 (March 2021).

Keiper, Felicity, and Ana Atanassova. Enabling genome editing for enhanced agricultural sustainability. *Frontiers in Genome Editing.* vol. 4, (May 2020).

Kemp, Luke, and others. Bioengineering horizon scan 2020. *ELife*, vol. *9*, (May 2020), pp. 1–20.

Kevin Schneider, and others. Insights on cisgenic plants with durable disease resistance under the European Green Deal. *Trends in Biotechnology*, vol. 41, No. 8 (August 2023), pp. 1027–1040.

Klümper, Wilhelm and Matin Qaim. A Meta-Analysis of the Impacts of Genetically Modified Crops. *PLoS ONE*, vol. 9 (November 2014).

Kosicki, Michael, Kärt Tomberg, and Allan Bradley. Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology*, vol. 36. (July 2018), pp. 765–771.

Kovak, Emma, Dan Blaustein-Rejto, and Matin Qaim. Genetically modified crops support climate change mitigation. *Trends in Plant Science*, vol. 27, No. 7 (July 2022), pp. 627–629.

Kumar, Krishan, and others. Genetically modified crops: current status and future prospects. *Planta*, vol. 251, No. 91 (March 2020).

Lawrenson, Tom, and others. Induction of targeted, heritable mutations in barley and Brassica oleracea using RNA- guided Cas9 nuclease. *Genome Biol*, vol. 16, No. 258 (November 2015).

Lee, Keunsub, and others. Activities and specificities of CRISPR/Cas9 and Cas12a nucleases for targeted mutagenesis in maize. *Plant Biotechnol J.*, vol. 17. No. 2 (February 2019), pp. 362–372.

Lema, Martin Alfredo. Regulatory aspects of gene editing in Argentina. *Transgenic Research,* vol. 28, (July 2019), pp. 147–150.

Lemke, Shawna, Xin Tao, and Gary Jay Kushner. Assuring the food safety of crops developed through breeding. *ACS Agricultural Science & Technology*, vol. 2, No. 6 (December 2022), pp. 1151–1165.

Lundgren, Jonathan G., and Jian J. Duan. RNAi-Based Insecticidal Crops: Potential Effects on Nontarget Species. *BioScience*, vol. 63, (August 2013), pp. 657–665.

Marone, Daniela, and others. From Transgenesis to Genome Editing in Crop Improvement: Applications, Marketing, and Legal Issues. *International Journal of Molecular Sciences*, vol. 24, No. 8 (March 2023).

Menz, Jochen, and others. Genome edited crops touch the market: A view on the global development and regulatory environment. *Frontiers in Plant Science,* vol. 11, No. 586027 (October 2020).

Mullins, Ewen, and others. Criteria for risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. *EFSA Journal*, vol. 20 (October 2022).

Napier, Johnathan A., and others. The challenges of delivering genetically modified crops with nutritional enhancement traits. *nature plants,* vol. 5 (June 2019), pp. 563–567.

Nekrasov, Vladimir, and others. Targeted mutagenesis in the model plant *Nicotiana benthamiana* using Cas9 RNA-guided endonuclease. *Nature Biotechnology,* vol. 31, No. 2655 (August 2013), pp. 691–693.

Norero, Daniel, Anna Maria Mastrangelo, and Grazia Maria Borrelli. GMO 25-year safety endorsement: 280 science institutions, more than 3,000 studies. Genetic Literacy Project, 21 January 2022.

Norris, Alexis L., and others. Template plasmid integration in germline genome-edited cattle. *bioRxiv*, vol. 38, No. 2 (July 2019), pp. 163–164.

Ono, Ryuichi. Double strand break repair by capture of retrotransposon sequences and reverse-transcribed spliced mRNA sequences in mouse zygotes. *Scientific Reports,* vol. 5, No. 12281 (July 2015).

_____. Exosome-mediated horizontal gene transfer occurs in double-strand break repair during genome editing. *Communications Biology,* vol. 2, No. 57 (February 2019).

Ortega, David L., Wen Lin, and Patrick S. Ward. Consumer acceptance of gene-edited food products in China. *Food Quality & Preference,* vol. 95, No. 104374 (2022).

Pellegrino, Elisa, and others. Impact of genetically engineered maize in agronomic, environmental and toxicological traits: A meta-analysis of 21 years of field data. *Scientific Reports.* Vol. 8, No. 3113 (February 2018).

Peterson, Brenda A., and others. Genome-wide assessment of efficiency and specificity in CRISPR/Cas9 mediated multiple site targeting in Arabidopsis. *PLoS ONE,* vol. 11, No. 9 (September 2016).

Petri, Karl, and others. CRISPR prime editing with ribonucleoprotein complexes in zebrafish and primary human cells. *National Biotechnology,* vol. 40, No. 2 (February 2022), pp. 189–193.

Phippen, Winthrop B., and others. From farm to flight: CoverCress as a low carbon intensity cash cover crop for sustainable aviation fuel production, A review of progress towards commercialisation. *Frontiers in Energy Research,* vol. 24, No. 793776 (June 2022).

Pixley, Kevin V., and others. Genome-edited crops for improved food security of smallholder farmers. *Nature Genetics*, vol. 54 (April 2022), pp. 364–367.

Qaim, Matim. Role of new plant breeding technologies for food security and sustainable agricultural development. *Applied Economic Perspectives & Policy,* vol. 42, No. 13044 (April 2020), pp. 129–150.

Ramirez-Torres, Fabiola, and others. Genome editing in fruit, ornamental, and industrial crops. *Transgenic Research*, vol. 30, (April 2021), pp. 499–528.

Ribarits, Alexandra, and others. Genome-Edited Plants: Opportunities and Challenges for an Anticipatory Detection and Identification Framework. *Foods*, vol. 10, No. 430 (February 2021).

Rodriguez, Angela Vega, and others. Myths and realities about genetically modified food: A risk-benefit analysis. *Applied Sciences*, vol. 12, No. 2861 (March 2022).

Rukavtsova, Elena B., and others. CRISPR-Cas genome editing for horticultural crops improvement: Advantages and prospects. *Horticulturae,* vol. 9, No. 38 (December 2022).

Sami, Abdul, and others. CRISPR–Cas9-based genetic engineering for crop improvement under drought stress. *Bioengineered,* vol. 12, No. 1 (September 2021), pp.5814–5829.

Shelton, Anthony M., and others. Bt brinjal in Bangladesh: The first genetically engineered food crop in a developing country. *Cold Spring Harbour Perspectives in Biology*, vol. 11 (June 2019).

Shigi, Ryoma, and Yuna Seo. Consumer acceptance of genome-edited foods in Japan. *Sustainability,* vol. 15, No. 9662 (June 2023).

Shukla, Vipula K., and others. Precise genome modification in the crop species *Zea mays* using zinc-finger nucleases. *Nature,* vol. 459, No. 7245 (May 2009), pp. 437–441.

Simeonov, Dimitre R., and others. A large CRISPR-induced bystander mutation causes immune dysregulation. *Communications Biology*, vol. 2, No. 70 (February 2019).

Simkin, Andrew John. Genetic Engineering for Global Food Security: Photosynthesis and Biofortification. *Plants*, vol. 8, No. 12 (December 2019).

Smyth, Stuart J. Contributions of genome editing technologies towards improved nutrition, environmental sustainability and poverty reduction. *Frontiers in Genome Editing*, vol. 4, (March 2022).

Sprink, Thorben, Ralf Wilhelm, and Frank Hartungand. Genome editing around the globe: An update on policies and perceptions. *Plant Physiology,* vol. 190, No. 3 (November 2022), pp. 1579–1587.

Strobbe, Simon, and others. Public acceptance and stakeholder views of gene edited foods: A global overview. *Trends in Biotechnology*, vol. 41, No. 6 (January 2022), pp. 736–740.

Talakayala, Ashwini, Sumalatha Katta, and Mallikarjuna Garladinne. Genetic engineering of crops for insect resistance: An overview. *Journal of Biosciences*, vol. 34, No. 114 (September 2020).

The Royal Swedish Academy of Sciences. Genetic scissors: A tool for rewriting the code of life. The Nobel Prize in Chemistry 2020.

Third World Network. Why Genome Edited Organisms are not Excluded from the Cartagena Protocol on Biosafety. Biosafety information Center, 11 December 2020.

Tripathi, Savarni, Jon Suzuki, and Dennis Gonsalves. Development of genetically engineered resistant papaya for papaya ringspot virus in a timely manner: a comprehensive and successful approach. *Methods in Molecular Biology,* vol. 354 (2007), pp.197–240.

Tsuda, Mai, Kazuo N. Watanabe, and Ryo Ohsawa. Regulatory status of genome-edited organisms under the Cartagena Act. *Frontiers in Bioengineering and Biotechnology*, vol. 7, No. 387 (December 2019).

Tuladhar, Rubina, and others. CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. *Nature Communications*, vol. 10, No. 4056 (September 2019).

Van Eck, Joyce. Applying gene editing to tailor precise genetic modifications in plants. *Journal of Biological Chemistry*, vol. 295, No. 38 (September 2020), pp. 13267–13276.

Vasquez, Oswaldo, Hayley Hesseln, and Stuart J. Smyth. Canadian consumer preferences regarding gene-edited food products. *Frontiers in Genome Editing*, vol. 4, No. 854334 (April 2022).

Venezia, Matthew, and Kate M. Creasey Krainer. Current advancements and limitations of gene editing in orphan crops. *Frontiers in Plants Science*, vol. 12 (September 2021).

Voytas, Daniel. Potential impacts of genome editing on climate adaptation and mitigation. SOAR Foundation. report, 27 September 2022.

Waltz, Emily. GABA enriched tomato is the first CRISPR-edited food to enter the market. *Nature Biotechnology*, vol. 40, No. 1 (January 2022), pp. 9–11.

Whelan, Augustina L., Patricia Gutti, and Martin A. Lema. Gene editing regulation and innovation economics. *Frontiers in Bioengineering and Biotechnology*, vol. 8, No. 303 (April 2020).

Wilhelm, Ralf, and others. Bericht zu möglichen Synergien der Nutzung neuer molekularbiologischer Techniken für eine nachhaltige Landwirtschaft. *OA open agrar*, vol. 215, (2021).

Wolt, Jeffrey D., and others. Achieving plant CRISPR targeting that limits off-target effects. *Plant Genome*, vol. 9, No. 3 (November 2016), pp. 1–8.

Wu, Katherine J. Crispr Gene Editing Can Cause Unwanted Changes in Human Embryos, Study Finds. The New York Times, 31 October 2020.

Zhang, Qiang, and others. Potential high-frequency off-target mutagenesis induced by CRISPR/Cas9 in Arabidopsis and its prevention. *Plant Molecular Biology*, vol. 96, No. 4-5, March 2018, pp. 445–456.

Zhu, Changfu, and others. Characteristics of genome editing mutations in cereal crops. *Trends Plant Sci*, vol. 22, No. 1 (January 2017), pp. 38–52.

F. Transient modification of agricultural plants, pests and pathogens using RNA interference or nanomaterials

Abdellatef, Eltayb, and others. Silencing the expression of the salivary sheath protein causes transgenerational feeding suppression in the aphid *Sitobion avenae. Plant biotechnology journal*, vol. 13, No. 6 (January 2015), pp. 849–857.

Aline Kotch. Chapter 8 - Development of RNAi-based biopesticides, regulatory constraints, and commercial prospects. *development and commercialization of biopesticides*, (April 2022), pp.149–171.

Arpaia, Salvatore, and others. Biosafety of GM Crop Plants Expressing dsRNA: Data requirements and EU regulatory considerations. *Frontiers in Plant Science*, vol. 11, No. 940 (June 2020).

Arpaia, Salvatore, and others. Environmental safety assessment of plants expressing RNAi for pest control. *in RNAi for Plant Improvement and Protection*. Syngenta, Ghent Innovation Center, Aarhus University, April 2021.

Australia, Office of the Gene Technology Regulator. *Overview - Status of Gene Editing and Other New Technologies*. October 2021.

Canada, Health Canada Food and Nutrition. *Novel Food Information - Improved Fatty Acid Profile Soybean MON 87705*. Ottawa, 2015.

Christiaens, Olivier, and others. Implementation of RNAi-based arthropod pest control: environmental risks, potential for resistance and regulatory considerations. *Journal of Pest Science*, vol. 95, No. 1 (January 2022).

Fletcher, Stephen J., and others. A Perspective on RNAi-based Biopesticides. Frontiers *in Plant Science*, vol. 11 (February 2020).

Food Standards Australia New Zealand. Response to Heinemann et al on the regulation of GM crops and foods developed using gene silencing. May 2013. Available at https://www.foodstandards.gov.au/consumer/gmfood/Response-to-Heinemann-et-al-on-the-regulation-of-GM-crops-and-foods-developed-using-gene-silencing.

Friends of the Earth. Gene-Silencing Pesticides Risk Health, Environment. report, 6 October 2020.

Greenlight Biosciences. International crop network validates ledprona as a new Mode of Action group. 4 May 2022.

Heinemann, Jack A. Should dsRNA treatments applied in outdoor environments be regulated? *Environment International*, vol. 132, No.104856 (November 2019).

Heinemann, Jack A., and Sophie Walker. Environmentally applied nucleic acids and proteins for purposes of engineering changes to genes and other genetic material. *Biosafety and Health*, vol. 1, No. 3 (December 2019), pp. 113–123.

Hernández-Soto, Alejandro, and Randall Chacón-Cerdas. RNAi Crop Protection Advances. *International Journal of Molecular Sciences*, vol. 22, No. 12148 (November 2021).

Hoang, Bao Tram L., and others. RNAi as a Foliar Spray: Efficiency and Challenges to Field Applications. *Molecular Sciences*, vol. 23, No. 6639 (June 2022).

Hung, Yu-Hung, and R Keith Slotkin. The initiation of RNA interference (RNAi) in plants. *Current Opinion in Plant Biology*, vol. 61, (June 2021).

Insect Resistance Action Committee. Mode of Action Classification Scheme. September 2023, available at https://irac-online.org/documents/moa-classification/.

James A. Baum, and others. Control of coleopteran insect pests through RNA interference. *Nature Biotechnology*, vol. 25, No. 11 (November 2007), pp. 1322–1326.

Jonathan G. Lundgren and Jian J. Duan. RNAi-Based Insecticidal Crops: Potential Effects on Nontarget Species. *BioScience*, vol. 63, No. 8 (August 2018), pp. 657–665.

Julia W Pridgeon, and others. Topically applied AaeIAP1 double-stranded RNA kills female adults of Aedes aegypti. *Journal of Medical Entomology*, vol. 45, No. 3 (May 2008), pp. 414–420.

Kenya, National Biosafety Authority. *Summary of an Application for environment release, cultivation and placing on the market of cassava event 4046 varieties.* [Accessed 11 December 2023].

Khajuria, Chitvan, and others. Parental RNA interference of genes involved in embryonic development of the western corn rootworm, *Diabrotica virgifera virgifera* LeConte. *Insect biochemistry and molecular biology*, vol. 63, (August 2015), pp. 54–62.

Khajuria, Chitvan, and others. Development and characterization of the first dsRNA-resistant insect population from western corn rootworm, *Diabrotica virgifera virgifera* LeConte. *PLOS ONE*, vol. 13, No. 5 (May 2018).

Koch, Aline, and Michael Wassenegger. Host-induced gene silencing - mechanisms and applications. *New Phytologist*, vol. 321, No. 1 (March 2021), pp. 54–59.

Liu, Shaoshuai, and others. RNA-based technologies for insect control. *plant production Biotechnology Advances*, vol. 39, (2020).

Lucena-Leandro, Vivian S, and others. Current scenario of exogenously induced RNAi for Lepidopteran agricultural pest control: From dsRNA design to topical application. *International Journal of Molecular Sciences*, vol. *23*, No. 15836 (December 2022).

Maori, E., Galanty, Y., Pignocchi, C., Chaparro Garcia, A., & Meir, O. (2023). Modifying the specificity of plant non-coding RNA molecules for silencing gene expressions (U.S. Patent No. 11,555,199 b2). Tropic Biosciences UK Limited.
Maori, Eyal; Galanty, Yaron; Pignocchi, Cristina; Chaparro Garcia, Angela; Meir, Ofir (2019): MODIFYING THE SPECIFICITY OF PLANT NON-CODING RNA MOLECULES FOR SILENCING GENE EXPRESSION. Applied for by Tropic Biosciences UK Limited on 3/30/2019. App. no. 18786034.1. Patent no. EP3684930. C12N15/113, C12N15/11, C12N15/82.

Mendelsohn, Michael L., and others. Summary of Discussions From the 2019 OECD Conference on RNAi- based Pesticides. *Pathogen Interactions*, vol. 11 (May 2020).

Mezzetti, Bruno, and others. What is its position in agriculture? *Journal of Pest Science,* vol. 93, (May 2020), pp. 1125–1130.

Mitter, Neena, and others. Clay nanosheets for topical delivery of RNAi for sustained protection against plant viruses. *Nature Plants*, vol. 3, No. 16207 (January 2017).

Organisation for Economic Co-operation and Development. "Considerations for the Environmental Risk Assessment of the Application of Sprayed or Externally Applied ds-RNA-Based Pesticides". Available at https://one.oecd.org/document/env/jm/mono(2020)26/en/pdf.

_____. "Considerations for the Human Health Risk Assessment of Externally Applied ds-RNA-Based Pesticides". 30 August 2023. Available at https://one.oecd.org/document/ENV/CBC/MONO(2023)26/en/pdf.

_____. Guidance document on the exchange and use of international efficacy and crop safety data for minor uses. Document ENV/JM/MONO, 2 March 2022.

_____. "Initial recommendations on evaluation of data from the developmental neurotoxicity (DNT) In-vitro testing battery". 26 August 2022.

Papadopoulou, Nikoletta, and others. Risk Assessment Considerations for Genetically Modified RNAi Plants: EFSA's Activities and Perspective. *Frontiers in Plant Science*, vol. 11, No (April 2020).

Pia S. Menezes. RNAi-based biocontrol of pests to improve the productivity and welfare of livestock production. Applied Biosciences, vol. 1, No. 3 (October 2022), pp. 229–243.

Rodrigues-Silva, Paolo Lucas, and others. RNAi and Bt approaches to insect-pest control: analyses and perspectives on trends in global patent publications. *Biotechnology Research and Innovation*, vol. 6, No. 2 (2022).

Rodrigues, Thais B., and others. First sprayable RNA-based biopesticide product targets Proteasome Subunit Beta Type-5 in Colorado Potato Beetle (Leptinotarsa decemlineat). *Frontiers in Plant Science*, vol. 20, (November 2021).

Shabalina, Svetlana A., and Eugene V. Koonin. Origins and evolution of eukaryotic RNA interference. *Trends in Ecology and Evolution*, vol. 23, No. 10 (Oct 2008), pp. 578–587.

Sirinathsinghji, Eva. Transferring the laboratory to the wild: An emerging era of environmental genetic engineering. Third World Network, November 2019. Available at https://biosafety-info.net/wp-content/uploads/2019/11/Biosafety-briefing_From-lab-to-wild.pdf.

United States, Environment Protection Agency, Environmental risk assessment for a FIFRA Section 3 Registration of the New Product GS2 Formulation (Calantha) Containing Ledprona, (Washington, D.C., United States, 2023).

_____. Human Health Risk Assessment, Review of Product Characterisation and Manufacturing Process for the New end-use product, Calantha. EPA reg. number: 94614-2 (Washington, D.C., United States, 2023).

_____. Pesticide Product Registration; Receipt of Application from GreenLight Biosciences to Register Ledprona as a New Active Ingredient (94614-R; 94614-E), (Washington, DC, 2021)

United states, Environmental Protection Agency. *EPA Opens Public Comment Period on Proposal to Register Novel Pesticide Technology for Potato Crops*. Washington, DC, 29 September 2023.

_____. Proposed Registration Decision for the New Active Ingredient Ledprona (Leptinotarsa decemlineata-specific recombinant double-stranded interfering Oligonucleotide GS2) in GS2 Formulation and GS2 Technical (CAS Number: 2433753-68-3), 2023.

Urquhart, William, and others. A novel method of demonstrating the molecular and functional equivalence between in vitro and plant-produced double-stranded RNA. *Regulatory Toxicology and Pharmacology*, vol. 73, No. 2 (November 2015), pp. 607–612.

Zhu, Kun Yan, and Subba Reddy Palli. Mechanisms, Applications, and Challenges of Insect RNA Interference. *Annual Review of Entomology*, vol. 65, (January 2020), pp. 293–311.

G. Technical refinement of novel delivery systems and chemistries to modify organisms in the field or in nature

Clube, J., Sommer, M., Grøndahl, C., & Van Der Helm, E. (2019). Altering microbial populations and modifying microbiota (U.S. Patent No. 10.463.049). United States Patent and Trademark Office.

Farzadfard, Fahim, and others. Efficient retroelement-mediated DNA writing in bacteria. *Cell Systems*, vol. 12, No. 9 (September 2022), pp. 860–872. Doi: 10.1016/j.cels.2021.07.001

Gaëtan, Burgio, and Lydia Teboul. Anticipating and Identifying Collateral Damage in Genome Editing. *Trends in Genetics*, vol. 36, No. 12 (October 2020), pp. 905–914.

Heidi Redford. CRISPR gene editing in human embryos wreaks chromosomal mayhem. *Nature*, vol. 583, No. 7814 (July 2020), pp. 17–18.

Heinemann, Jack A., and others. Differentiated impacts of human interventions on nature: Scaling the conversation on regulation of gene technologies. *Elementa*, vol. 9, No. 1 (March 2021). Imperial College London, Conrad Duncan. Scientists discover new approach to fighting antibiotic resistance. 24 February 2022.

Li, Tingdong, and others. Highly efficient heritable genome editing in wheat using an RNA virus and bypassing tissue culture. *Molecular Plant*, vol. 14, No. 11 (July 2014), pp. 1787–1798.

Liu, Qian, and others. Engineered biocontainable RNA virus vectors for non-transgenic genome editing across crop species and genotypes. *Molecular Plant*, vol. 16, No. 3 (February 2023), pp. 616––631.

Ma, Xiaonan, and others. Highly efficient DNA-free plant genome editing using virally delivered CRISPR–Cas9. *Nature Plants*, vol. 6, No. 7 (June 2020), pp.773–779.

National Academy of Medicine, National Academy of Sciences, and the Royal Society. *Heritable Human Genome Editing*. National Academies Press, Washington, DC, September 2020.

Rubin, Benjamin E., and others. Species- and site-specific genome editing in complex bacterial communities. *Nature Microbiology*, vol. 7, No. 1 (December 2021), pp. 34–47.

Sirinathsinghji, Eva. Transferring the laboratory to the wild: An emerging era of environmental genetic engineering. Third World Network, November 2019. Available at https://biosafety-info.net/wp-content/uploads/2019/11/Biosafety-briefing_From-lab-to-wild.pdf.

Trafton, Anne. Artificial intelligence yields new antibiotic. MIT News, Massachusetts Institute of Technology, 20 February 2020.

_____. Metabolic mutations help bacteria resist drug treatment. MIT News, Massachusetts Institute of Technology, 18 February 2021.

_____. New method opens the door to efficient genome writing in bacteria. Massachusetts Institute of Technology, 5 august 2021.

_____. Using AI, scientists find a drug that could combat drug-resistant infections. MIT News Massachusetts Institute of Technology, 25 May 2023.

H. Ability to re-create viruses by chemical DNA synthesis

Cello, Jeronimo, Aniko V. Paul, and Eckard Wimmer. Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template. *Science*, vol. 297, No. 5583 (July 2022), pp. 1016–1018.

DeFrancesco, Laura. Synthetic virology: the experts speak. *Nature biotechnology*, vol. 39 (October 2021), pp. 1185–1193.

Guenther, Caitlin M., and others. Synthetic virology: engineering viruses for gene delivery. *WIREs Nanomed Nanobiotechnol*, vol. 6, No. 1287 (September 2014), pp. 548–558.

Inglesby, Tom. Horsepox and the need for a new norm, more transparency, and stronger oversight for experiments that pose pandemic risks. *PLOS Pathogens*, vol. 10, No. 1371 (October 2018).

Thao, Tran Thi Nhu, and others. Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform. *Nature*, vol. 582, (May 2020), pp. 561–565.

Tumpey, Terrence M., and others. Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus. *Science*, vol. 310, No. 5745 (October 2005), pp. 77–80.

United Nations, Convention on Biological Diversity. *Biosafety Technical Series, No. 100*. April 2022.

United States of America, Department of Health and Human Services. *Screening framework guidance for providers of synthetic double-stranded DNA*. Available at https://www.phe.gov/preparedness/legal/guidance/syndna/documents/syndna-guidance.pdf.

Venter, Craig J., and others. Synthetic chromosomes, genomes, viruses, and cells. *Cell Press*, vol. 185 (July 2022), pp. 2708—2724.

Wimmer, Eckard, and others. Synthetic viruses: a new opportunity to understand and prevent viral disease. *Nature Biotechnology*, vol. 27, (December 2009), pp. 1163–1172.

I. Interaction of synthetic biology organisms in the environment and potential for cumulative effects

Connolly, John B., and others. Recommendations for environmental risk assessment of gene drive applications for malaria vector control. *Malaria Journal*, vol. 21, No. 152 (May 2022).

European Food Safety Authority, Devos, Yann, and others. 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 Journal*, vol. 17, No. 11 (November 2020).

Hayes, Keith, and others. Risk assessment for controlling mosquito vectors with engineered nucleases: Sterile male construct Final report. CSIRO Research Publications Repository, Foundation for the National Institutes of Health. Hobart, Australia, 2023.

Heinemann, Jack A., and others. Differentiated impacts of human interventions on nature: Scaling the conversation on regulation of gene technologies. *Elementa Science of the Anthropocene,* vol. 9, No. 1 (March 2017).

Hosack, Geoff, and others. Risk assessment for controlling mosquito vectors with engineered nucleases: Paternal male bias construct. *in CSIRO Research Publications Repository***,** EP2022-4945, (Hobart, Australia, 2023).

Keith Hayes, and others. Structured prioritisation of human and animal pathogens for the purpose of scoping risk assessments of genetic control strategies for malaria vectors in sub-Saharan Africa Final report. CSIRO Research Publications Repository. Hobart, Australia, 2020.

Koller, Franziska, and others. The need for assessment of risks arising from interactions between NGT organisms from an EU perspectiv*e. Environmental Sciences Eur*ope, vol. 35, No. 27 (April 2023).

United Nations, Convention on Biological Diversity. Summary of discussions of the Open-ended Online Forum on Synthetic biology. 2022.

Webb, Cameron E., Philippe G. Porigneaux, and David N. Durrheim. Assessing the risk of exotic mosquito incursion through an international seaport, Newcastle, NSW, Australia. *Tropical Medicine and Infectious Disease*, vol. 6, No. 25 (February 2021).

J. Transboundary movements and relation to detection and identification of synthetic biology organisms, parts and products

Backus, Greogry A., and Jason A. Delborne. Threshold-dependent gene drives in the wild: Spread, controllability, and ecological uncertainty. *BioScience*, vol. 169, No. 11 (November 2019), pp. 900–907.

Ifakara Health Institute, the Foundation for the National Institutes of Health & Gene Convene. Gene drives for malaria elimination: A masterclass with global experts and African malaria leaders. YouTube video, 22 June 2023.

Li, Liang, and others. Application of Sampling and Detection Methods in Agricultural Plant Biotechnology. *Science Direct*, (2022), pp. 67–84.

De Graeff, Nienke, and others. The boundary problem: Defining and delineating the community in field trials with gene drive organisms. *Bioethics*, vol. 37, No. 6 (May 2023), pp. 600–609.

J, Wu, and others. Stability of genomic DNA at various storage conditions. Poster presented at the International Society for Biological and Environmental Repositories, Sera Care Life Sciences, 2009.

Shillito, Ray. Chapter 12 - International standards and guidelines. in Application of Sampling and Detection Methods. i*n Agricultural Plant Biotechnology*. BASF Corporation, NC, United States, 2022).

United Nations, Convention on Biological Diversity, Treaty Series, vol. 1760, No. 30619.

World Health Organization. *Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research*. Geneva, September 2022. Available at https://www.who.int/publications/i/item/9789240056107.

Sera Care Life Sciences & Biorepository. Stability of Genomic DNA at Various Storage Conditions. Presented at the ISBER 2009 Conference. Available at https://www.colorado.edu/ecenter/sites/default/files/attached-files/seracare_stability_of_genomic_dna_at_various_storage_conditions_isber2009.pdf.

K. Increased field testing of synthetic biology applications, including in areas outside the national jurisdiction of the developer or funder

Connolly, John B., and others. Recommendations for environmental risk assessment of gene drive applications for malaria vector control. *Malaria Journal*, vol. 21, No. 152 (May 2022).

Glandorf, Boet. Technical evaluation of a potential release of OX513A *Aedes aegypti* mosquitoes on the island of Saba. National Institute for Public Health and the Environment, (2017), pp. 1–71.

ISAAA and Outreach Network for Gene Drive Research. Field evaluations of gene drive organisms. 2023. Available at https://genedrivenetwork.org/resources/policy-briefs/47-isaaa-policy-brief-3-field-trials/file.

Long, Kanya C., and others. Core commitments for field trials of gene drive organisms. *Science*, vol. 370, No. 6523 (December 2020), pp. 1417–1419.

Oxitec, OX513A Technical Dossier, 2016.

L. Dual-use nature and biosecurity implications of synthetic biology

Eckard Wimmer. Synthetic biology, dual use research, and possibilities for control. *in NATO Science for Peace and Security Series A: Chemistry and Biology.* Vladan Radosavljevic, Ines Banjari, Goran Belojevic, eds. Springer Dordrecht, March 2018.

Jennings, Bruce. Unnatural Selection. Vanderbilt University, blog, 4 July 2016.

Kaebnick, Gregory E., and others. Precaution and governance of emerging technologies. *Science*, vol. 354, No. 6313 (November 2016), pp. 71–711.

National Academies of Sciences, Engineering, and Medicine. *Biodefense in the age of synthetic biology*. Washington, DC.: The National Academies Press, 2018.

National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* Washington, DC.: The National Academies Press, 2016.

Patrone, Daniel, David Resnik, and Lisa Chin. Biosecurity and the Review and Publication of Dual-Use Research of Concern. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, vol. 10, No. 3 (September 2012), pp. 290–298.

Roberts, Aaron J. "Ethical analyses concerning the development and use of gene drive modified mosquitoes for malaria elimination". Master's thesis, McMaster University, 2022. Available at https://macsphere.mcmaster.ca/handle/11375/28038.

United Nations, Educational, Scientific and Cultural Organization, World Commission on the Ethics of Scientific Knowledge and Technology. *The precautionary principle*. Available at https://unesdoc.unesco.org/ark:/48223/pf0000139578.

Wareham, Christopher, and Cecilia Nardini. Policy on synthetic biology: Deliberation, probability, and the precautionary paradox. *Bioethics*, vol. 29, No. 2 (November 2013), pp. 118–125.

World Health Organization. *Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research*. Available at https://www.who.int/publications/i/item/9789240056107.

_____. *Guidance framework for testing genetically modified mosquitoes*. second eds. Geneva. Available at https://www.who.int/publications/i/item/9789240025233.