Environmental Risk Assessment (ERA)

Environmental Risk Assessment (ERA) is a well-established structured process involving the collection of empirical data, as well as technical information, such as computational modelling and literature reviews, to provide a basis for assessing, either quantitatively and/or qualitatively, the potential for activities to cause harm to "protection goals".

Protection goals involve people, animals, or the environment that we want to protect from harm and are generally derived from national government regulations or policy. They may also consider specific regional priorities, as well as issues identified through community and stakeholder engagement.

ERA is undertaken on a case-by-case basis for each application of activities, at each stage of research to inform decisions of the project and national regulatory authorities and to communicate to stakeholders. ERA can be conducted by developers, independent parties, or by national regulatory bodies. In some cases, it is a legal requirement to submit an ERA document for evaluation by government authorities as part of the submission process.

As Target Malaria looks towards ERA for gene drive applications, we are seeking emerging guidance to ensure our processes are aligned with relevant recommendations, such as inclusion of a broad range of expertise and stakeholder input in different stages of the process (see Connolly *et al* 2022).

Three concepts are fundamental to ERA:

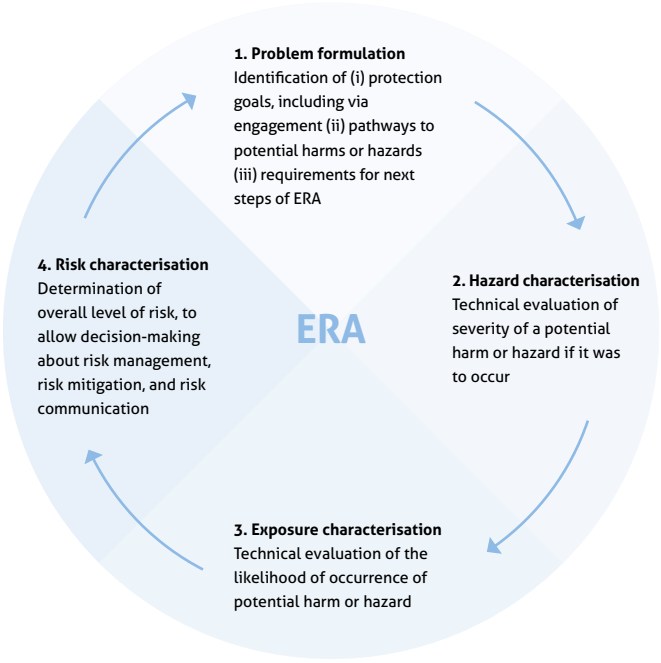
- **Hazard:** Anything that could cause potential harms or adverse effects. These could be direct or indirect and is usually linked to the nature of the organism under evaluation.
- **Exposure:** These are the routes and extent to which someone or something is subjected to the hazard.
- **Risk:** A function of both the hazard and the exposure and related to the chance that someone or something (i.e., a protection goal) will be harmed.

In the case of Target Malaria research activities, ERA will be specific to a genetically modified mosquito strain proposed for introduction into a specific location, which establishes the spatial and temporal boundaries for the ERA.

Understanding the risk profile of the various strains of genetically modified mosquitoes is fundamental to Target Malaria's decision making and includes the assessment and management of risk throughout our phased development pathway.

ERA is carried out on a case-by-case basis as it needs to consider the genetic modification(s) made and the resulting phenotype, the species of organism, the receiving environment, the scope, and experimental design of the proposed field study, as well as local control measures in place.

Taken together the ERA process involves four fundamental steps, each of which can be iterative and built on previous stages:



Stage 1: Problem formulation

ERA starts with a rigorous and systematic scientific analysis known as "problem formulation" that defines the parameters of the risk assessment in consideration of the defined protection goals. Protection goals are drawn from policy, legislation, regulatory documents, and community interactions and are often high level and conceptual. To be useful in risk assessment they need to be translated into specific operational goals for which risk assessment endpoints can be identified.

In the problem formulation stage, a wide range of potential harms are identified with expert inputs, and a plausible pathway to potential harm can be conceptualised establishing the causal chain of events required for that harm to be realised. Some potential identified harms will not result in a biologically plausible pathway and can be excluded at an early stage in the ERA. These should be captured and documented however as part of the process.

Stage 2: Hazard characterisation

Following completion of stage 1, problem formulation, specific hazards and exposure scenarios can be evaluated and characterised to come up with an overall estimate of risk. In characterising a hazard, risk assessors are interested in the potential consequences of exposure to a hazard, that is, the *severity of potential harm, damage, or adverse effect to the environment or health.*

Stage 3: Exposure characterization

In characterising exposure, risk assessors are interested in the *likelihood that a particular hazard will occur.*

Stage 4: Risk characterization

Taken together, risk is the *product of the likelihood of a particular hazard occurring and, if it occurs, the magnitude of harm that it might cause.*

Risk is often qualified in a matrix such as that presented below.

		RISK ESTIMATE			
Likelihood assessment (exposure)	Highly likely	Low	Moderate	High	High
	Likely	Low	Low	Moderate	High
	Unlikely	Negligible	Low	Moderate	Moderate
	Highly unlikely	Negligible	Negligible	Low	Moderate
		Marginal	Minor	Intermediate	Major
		CONSEQUENCE ASSESSMENT (HAZARD)			

Risk matrix to estimate the level of risk from a combination of outcomes of likelihood (exposure) and consequence (hazard) assessments. (Adopted from the Australian Department of Health, Office of the Gene Technology Regulator MONITORING AND COMPLIANCE RISK ANALYSIS PROTOCOL In accordance with the Gene Technology Act 2000 (2016))

International framework for ERA of living modified organisms

The **Cartagena Protocol on Biosafety to the Convention on Biological Diversity** is an international agreement that aims to ensure the safe handling, transport, and use of living modified organisms (LMO) developed by using modern biotechnology techniques. It has currently been adopted in over 173 countries (https://bch.cbd.int/protocol/).

The African countries where Target Malaria currently operates have ratified the Cartagena Protocol, and have translated, or are in the process of translating the Protocol into national laws, regulations, and guidance documents for how LMO's should be assessed and managed.

The Protocol includes explicit requirements for the use of LMOs and has a dedicated Annex for ERA (Annex III)[1]. The general principles for ERA are stated as follows:

1. Risk assessment should be carried out in a scientifically sound and transparent manner, and can consider expert advice of, and guidelines developed by, relevant international organizations.
2. Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk.
3. Risks associated with living modified organisms or products thereof, namely, processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained using modern biotechnology, should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.
4. Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature and level of detail from case to case, depending on the living modified organism concerned, its intended use and the likely potential receiving environment.

National and international expert bodies have also started to consider if engineered gene drives (which meet the definition of Living Modified Organisms under the Cartagena Protocol), raise new or different questions and whether current guidance for risk assessment needs updating[2]. Emerging themes regarding the risk assessment of gene drives include:

- Case by case assessment remains important and current risk assessment frameworks are largely adequate but there may be certain areas that need additional guidance.
- Consideration of socio-economic impacts and public participation in decision making.
- Quantitative risk assessment tools and modelling will become more prevalent in risk assessment.
- Additional guidance may be required for the evaluation of molecular biology.
- New tools and/or methodologies may be required for post release monitoring.

Target Malaria closely monitors emerging developments in the field of ERA for gene drive and we seek to incorporate appropriate recommendations in our planning and assessment activities.

1 https://bch.cbd.int/protocol/text/

2 https://www.efsa.europa.eu/en/efsajournal/pub/6297
https://www.cbd.int/doc/decisions/cp-mop-10/cp-mop-10-dec-10-en.pdf
https://www.ncbi.nlm.nih.gov/books/NBK379271/

References

Connolly, J.B., Mumford, J.D., Glandorf, D.C.M. et al. Recommendations for environmental risk assessment of gene drive applications for malaria vector control. *Malar J* **21**, 152 (2022). *https://doi.org/10.1186/s12936-022-04183-w*

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

Target Malaria Factsheet: *International policy framework for genetically modified mosquitoes* factsheet for complementary information: *https://targetmalaria.org/wp-content/uploads/2022/08/Reg_FS_EN_InternationalPolicy-_Aug22.pdf*

Blog: *https://targetmalaria.org/how-to-advance-environmental-risk-assessment-of-gene-drive-for-malaria-when-its-never-been-done-before/*