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Moving towards Safe(r) Innovation Approach in the context of modern biotechnology

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Foreword

The OECD Working Party on Harmonisation of Regulatory Oversight in Biotechnology (WP-HROB) and the OECD Working Party for the Safety of Novel Foods and Feeds (WP-SNFF) serve as forums for exchanging approaches and experience in environmental risk/safety assessments of organisms produced through modern biotechnology, aiming to improve mutual understanding and to increase the efficiency of the assessments. They identify and address issues from the development and application of biotechnology, aiming to facilitate harmonisation in risk/safety assessments, while promoting the safe use.

This document deals with the conceptual framework on Safe(r) Innovation Approach for products of modern biotechnology. Its purpose is to:

- present and illustrate the concept of Safe(r) Innovation Approach in modern biotechnology and elements of its possible application in practice;
- foster the design of innovative products to address foreseeable safety issues, the navigation of the regulatory pathway, and the deployment of stakeholder engagement(s), from the earliest phases of product development throughout the lifecycle of the product, thereby supporting responsible use.

This document does not serve as guidance to regulators or as guidance for risk/safety assessments, nor is it intended to replace (components of) risk assessment.

Given the rapid evolution of modern biotechnology and the continuous development of new scientific knowledge, analytical tools, regulatory practices, and engagement models, this document should be considered evergreen. To maintain its relevance and utility, the Working Parties (HROB, SNFF) may incorporate new examples or other revisions based on new knowledge, emerging risks, evolving methodologies and tools, and changes in the regulatory landscape. Such updates will help ensure that the Safe(r) Innovation Approach remains aligned with scientific and technological progress and continues to support developers and regulators through relevant and practically applicable considerations.

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1 Introduction

Aim and focus

This document introduces the concept of the Safe(r) Innovation Approach (SIA) in the field of modern biotechnology. It shows how elements of SIA can support and strengthen the development process of biotechnology products from the earliest design phases throughout the life cycle at the level of safety.

The SIA document is aimed at those engaged in development activities of new products with genetically modified organisms (referred to as “developers”). This document might be most relevant for developers new to the field, or developers engaged in the development of organisms or traits for which there is relatively little experience.

The design and development process of biotechnology products is not necessarily linear but may be iterative. This document demonstrates that the SIA concept fits well into this iterative nature of the development process and illustrates with two product examples its application by developers[1].

This document does not serve as guidance to regulators or for risk/safety assessments and is not intended to add to or replace regulatory frameworks. Instead, it presents a compilation of best practices reflective of the concept of SIA.

Safe(r) Innovation Approach in the context of modern biotechnology

There is a long tradition of risk/safety awareness in the field of modern biotechnology. The safety of the resulting products for human health and the environment is established by following risk/safety assessment principles and approaches that are laid down in key OECD documents (OECD, 1986; OECD, 1993; OECD, 2023) and applied in existing regulatory frameworks. It has been recognised that biotechnological innovation is continuous, with an increasing diversity of developers and expanding range of potential applications and products. As illustrated for other fields, such as chemistry and nanomaterials, the Safe(r) Innovation Approach (SIA)[2] is intended to share knowledge and provide tools for developers for considering potential safety challenges in biotechnological innovations.

Achieving safety for human/animal health and the environment of products of modern biotechnology has been accomplished by addressing safety concerns early on in the development process, and on final

[1] The examples in this document fall within the primary areas of interest of WP-HROB and WP-SNFF, namely biotechnology applications in agriculture and/or the environment, although biotechnology applications can impact several industry sectors like environmental, agricultural, medical, industrial, informatics, etc.

[2] The SIA approach has also been considered in other OECD working groups and is a broader concept that spans multiple fields, such as nanomaterials, chemistry, neurotechnology, and anticipatory governance of emerging technologies (OECD 2020; 2021; 2024a; 2024b). The elements of the SIA approach described in figure 1 are tailored to the field of biotechnology, however, they are closely related to the elements of ‘Safe(r)-by-Design’, ‘Regulatory Preparedness’ and ‘Trusted Environment’ described In SIA for nanomaterials and nano-enabled products (OECD, 2020).

evaluations prior to commercialisation. However, so far, this process has mainly been a reactive process, addressing safety issues as they arise. The SIA transforms product development from a reactive process to a more proactive approach that anticipates and addresses safety issues throughout every stage of product development. This involves developers considering questions such as: Which components of the designed product may pose potential safety issues to the environment and human health? How can the design be adapted to minimise such risks and/or exposure? How can adverse effects be prevented or controlled (van Gelder et al., 2021)? Such questions pre-empt those that are the basis of regulatory risk/safety assessment, therefore their consideration from the early stages of product development may assist developers navigating the applicable regulatory pathway for their product. Within the field of biotechnology, these types of questions are routine during product development. The concept of Problem Formulation can help to guide and structure their consideration (as described in Environmental considerations for risk/safety assessment for the release of transgenic plants (OECD, 2023)).

Although the term SIA is relatively new, elements of this concept have long been common practice for developers of modern biotechnology, a field with four decades of regulatory experience. This document provides a snapshot in time of the use of SIA elements by developers with the aim to illustrate how they can support and strengthen the process of development of safe(r) biotechnology products through increased awareness, collaboration and knowledge transfer.

For the purpose of this project, as shown in Figure 1, the SIA concept involves three pillars:

- considering safety in the design and throughout the lifecycle of a product to address risks to human health and the environment,
- navigating the regulatory process, and
- the deployment of stakeholder engagement(s).

As also shown in Figure 1, the SIA elements are interconnected in a non-linear, iterative process designed to facilitate transparent and consistent communication.

The interconnection of the three SIA pillars in Figure 1 enables developers to proactively identify and minimise possible human health and environmental risks of products of modern biotechnology through engagement with regulators and stakeholders in a non-linear, iterative process designed to facilitate transparent and consistent communication.

Safety considerations should preferably be systematically integrated by developers throughout the innovation process. Although the effectiveness of risk/safety considerations will be highest in the early phases of the innovation process, the SIA approach addresses the safety of the product and associated processes through the product’s lifecycle, from concept to commercialisation (OECD, 2020).

Navigating the regulatory process involves exchanges and knowledge sharing between regulators and developers. Such exchange enables regulators to anticipate new biotechnological innovations and provide early guidance on potential first-in-class products. In turn, it helps developers prepare for regulatory compliance through a better understanding of potential requirements, allowing them to navigate the regulatory process more smoothly.

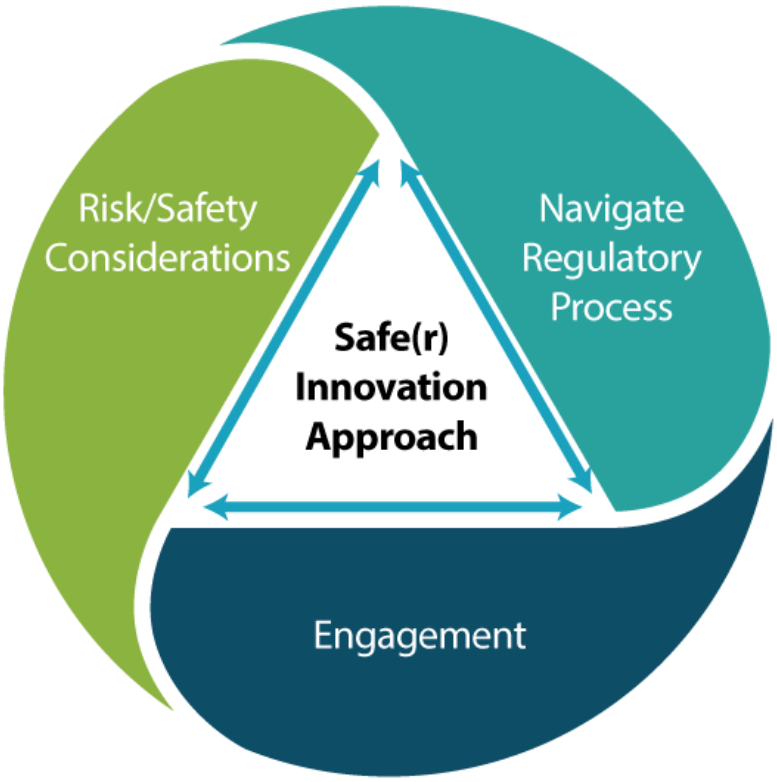
Stakeholder engagement initiated by developers can encompass dialogue and knowledge-sharing among regulators, developers, other stakeholders, and the public. These interest groups can inform about regulatory, social, ethical, ecological and economic factors, that can offer comprehensive insights on impacts and safety issues of a product or technology. SIA integrates these types of engagement, ideally from the early stages of product design and development, thus adding value to product development.

Another component of SIA is building trust. Trusted environment is a secured, confidential platform or framework that allows proactive risk assessment, faster innovation, and regulatory preparedness, while protecting intellectual property and competitive advantages. It enables dialogue and data sharing between

researchers, industry stakeholders, and regulators to identify and mitigate safety risks before, during, and after product development.

The principles and concepts of SIA overlap with those of Responsible Research & Innovation (RRI) (see Groenen et al., 2025; George et al., 2025) and responsible innovation (OECD, 2024; OECD, 2025), particularly for stakeholder engagement, in the context of modern biotechnology.

Figure 1. Schematic overview of the SIA pillars and their interconnection in the context of modern biotechnology



This document is structured as follows: Section 2 “Decision-making throughout the lifecycle of a biotechnology product” describes how SIA can inform decisions regarding the development path of a product and throughout its lifecycle. Section 3 “Tools, processes and procedures” provides general information on how the concept of SIA can be applied by developers in scoping design considerations regarding environmental and human health safety, in understanding of the regulatory landscape and in voluntary engagements. Section 4 provides two examples of applying SIA: one for a class of products with a history of safe use (insect-resistant maize) and another for a technology that is currently in development (engineered gene drives). The tables in Section 3 refer to the illustrative examples in Section 4, and together the Sections provide further details on how elements of SIA have been or could be applied.

2 Decision-making throughout the lifecycle of a biotechnology product

The generic development pathway and lifecycle for products of modern biotechnology is illustrated in Figure 2 and shows how the SIA concept can be part of a product's lifecycle to improve decision making. During the initial design phase, product concepts (ideas) are identified (Discovery phase). Some concepts may proceed to a Proof-of-Concept phase for deeper evaluation, paving the way for early research and development. In these early phases, risk/safety considerations are integrated into the process, including technical design aspects that are relevant for the product's safety. This may also be the stage where the likelihood of regulatory approval of the product is assessed, through developers' early engagements with regulators to understand the regulatory pathway and appropriate requirements. These engagements may be non-mandatory but helpful for developers to ensure regulatory compliance in various geographic regions where commercial releases are envisaged.

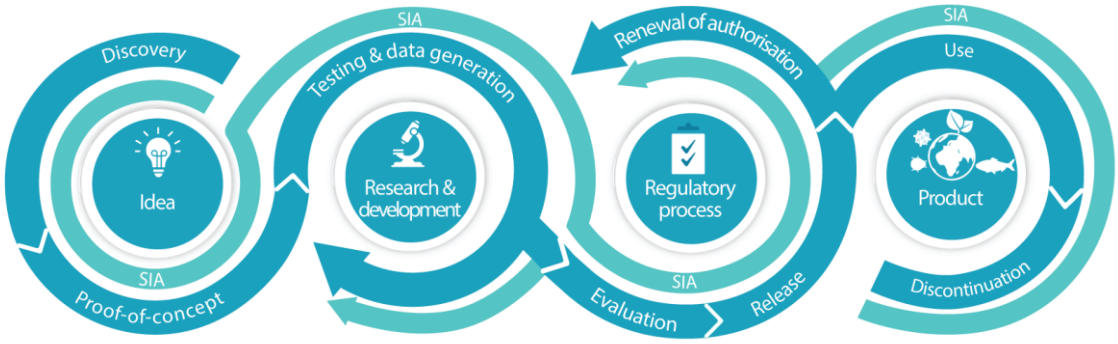
In the Testing and Data Generation phase, developers may generate information for demonstrating safety and if needed to optimise the technical design parameters of the product, and in some instances begin generating data for the regulatory dossier. Testing and optimalisation of the technical design is an iterative process, which may also include the voluntary engagement with end-users to consider their preferences or concerns for the product, with the community to understand product acceptance (or barriers to acceptance), and with regulators to understand potential regulatory requirements and enable a more predictable regulatory process.

When development is completed, the product enters the Evaluation phase of the regulatory process[3]. While the conceptual framework of SIA could support regulatory preparedness for emerging products in modern biotechnology, it is not intended to replace or to be incorporated into a regulatory regime for risk/safety assessment. Upon successful completion of the evaluation phase, the product can enter the Release and Use phases, in which considerations addressing the intended product use - such as stewardship plans (e.g., insect resistance management) or monitoring (e.g., of gene drives) - are deployed as needed. Post-market stewardship is not related to safety of the product itself but is intended to ensure the durability of the product and its potential beneficial environmental impact. In this phase there may be active engagement to adapt deployment, stewardship or monitoring programs based on the latest science and acquired experience. In jurisdictions with time-bound approvals, a Renewal of Authorisation phase might be applicable.

In the Discontinuation phase the product will be phased out. Knowledge gained during the product stage may inform developers in addressing risk/safety considerations during the design and development of future products.

[3] Regulatory processes may also apply before the completion of the development of the product. For instance, regulatory oversight and environmental assessment applies to investigational clinical trials before commercialisation, as well as to experimental field studies for gene drive insects.

Figure 2. Generic development pathway and lifecycle for products of modern biotechnology, and SIA's role throughout the lifecycle



3 Tools, processes and procedures

Scoping

At the idea stage, it is beneficial for developers to already start considering the entire lifecycle of a product and to leverage the three pillars of SIA (Figure 1) to address environmental and human health safety, plan voluntary engagements, and navigate the regulatory process. Common early-stage considerations include:

- Defining and clarifying the product and the protection goals which need to be addressed.
- Identifying various risk/safety considerations and how to appropriately address them.
- Acquiring an understanding of the regulatory landscape pertaining to the product including global regulatory processes, safety requirements, and timelines.
- Determining the degree to which voluntary engagement with regulators, other stakeholders, and the public may be needed, depending on the developer's experience level and the novelty of the technology. For example, technologies with novel risk/safety considerations (e.g., engineered gene drives; Section 4.2) may require more extensive engagement, while those with a history of safe use and regulator familiarity (e.g., insect-resistant maize; Section 4.1) may require less.

SIA can be thought of as a toolbox containing various tools, processes and procedures, including design considerations (see Table 1) and engagement (see Table 2), which developers may apply when considering different aspects of safety during product development. It is up to the developer to decide which of those tools in the toolbox are most suitable and proportionate to the case at hand. The examples in Section 4 illustrate this in more detail.

Risk/safety considerations

From the outset of product development, it is relevant to integrate considerations for environmental and human health safety, including thoughtful design strategies to address these concerns. The purpose and practical use of some of the design considerations that are described in the examples in Section 4 are summarised in Table 1 below. This table is intended to exemplify some aspects of technical design considerations as part of SIA during an innovation process of a biotechnology product. These factors may not be obvious at first and require developers to "think outside the box" and take time to consider the specific aspects of the product being developed (e.g., unique product concept or novel protein).

Table 1. Examples of (technical) design considerations as part of the SIA in biotechnology

Design considerations to address potential hazards or limit the level of exposure	
Risk/safety assessments aspects[4]:	**Examples of technical options to be applied on a case by case basis depending on the product:**
Reduction in non-target effects	• Leveraging the specificity of a transgenic protein to target outcome/species (IR maize example) • Selecting and modifying promoters to control where protein is expressed (IR maize example)
Spatial distribution of trait/organism	• Using designs to limit establishment of transgenic organisms (Gene drives example)
Temporal distribution of trait/organism	• Using designs which limit propagation of transgenic organisms to a time period (Gene drives example) • Selecting and modifying promoters to control when protein is expressed (Gene drives example)
Food allergenicity	• Using proteins with established safety and/or history of safe use (IR maize example) • Early R&D application of bioinformatic tools (IR maize example) • Assessing *in silico* allergenicity of candidate genetic sequence (IR maize example)
Food toxicity	• Using proteins with history of safe use (IR maize example) • Early R&D application of bioinformatic tools (IR maize example) • Assessing *in silico* toxicity of candidate genetic sequence (IR maize example)
Intraspecific/population-specific	• Using biological containment of the transgenic elements within a species, a specific population or a sex (Gene drives example)
Auxotrophy	• Leveraging lack of persistence of transgenic organisms in natural environment (Gene drives example)
Other safety-related design considerations:	
Aspect:	**Examples of other (non-)technical options:**
Reversion	• Restoration of unmodified population (Gene drives example)
Modular design approach	• Applying a modular design approach to perform field testing with self-spreading organisms (Gene drives example)
Balance risk-benefit	• Analysing trade-offs between agronomic trait performance and efficacy versus non-target organisms (IR maize example)
Consideration of monitoring programs	• Confirming conclusions of (environmental) risk assessment and/or reducing uncertainties regarding earlier identified potential risks

[4] This table could be expanded with other technical design considerations, for example by adding other areas of concern, such as potential changes to survival, persistence, and invasiveness of the product, effects on biogeochemical processes, or effects on human and animal health.

Engagement for navigating the regulatory process and engagement within the Safe(r) Innovation Approach in biotechnology

Stakeholder engagement initiated by developers can encompass dialogue and knowledge-sharing among regulators, developers, the public and other stakeholders. Engagement with stakeholders can support the SIA in several ways, through for example:

- Providing insight into regulatory risk/safety assessments of organisms resulting from modern biotechnology in the early stages of product design,
- providing insights into social, ethical and ecological concerns of public interest groups, which can offer insights into safety issues of a product that may not have been addressed,
- sharing knowledge with regulators about novel science and technology with which they may not have prior experience,
- identifying plausible pathways to harm through discussion with external experts, including regulators, that may not have been considered by developers and other stakeholders,
- adhering to requirements from regulators or other applicable industry standards in pre- and post-commercial release to address product use (e.g. resistance management).

SIA also presents developers with various options for voluntary engagements with regulators and the public (Table 2 consists of a variety of examples that have already been put in practice). For developers working on products for which there is less familiarity (i.e., little or no prior experience with the organism, genetic modification, or its intended use exists, or a combination of these factors), (early) engagement with regulatory bodies and other stakeholders may be helpful in clarifying the regulatory and safety requirements to be addressed during product development. In contrast, developers of familiar products may not need extensive engagement due to the existing understanding of the product. Table 2 provides a selection of engagements options that developers may consider.

Table 2. Types of voluntary engagement for consideration by product developers[5]

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
Early Public Engagement	This type of engagement is intended to introduce a public audience or stakeholder group to a proposed technology and its use. Feedback that can inform a SIA includes hearing from members of the public about their questions for the use of a technology, which may help to shape problem formulations and recognize protection goals and other values that should be considered during the design process. Transparent engagement processes can help to improve understanding of decisions during SIA.	When technologies or products are novel, or when the proposed use of the product is novel and when previous experience with risk/safety assessment, risk management and decision making may be lacking.	The early public engagements for the use of engineered gene drives for the control of malaria.	Early
Early Regulatory Engagement	Early consultative meetings and pre-submission meetings with regulatory agencies. Both developers and regulators clarify regulatory oversight and whether policies and guidance are available.	This would enable developers to predict and plan in a clearer way addressing regulatory requirements in the R&D process.	Pre-submission engagement procedures for novel foods, novel feeds, plants, animals or microorganisms with novel traits by the Canadian Food Inspection Agency and Health Canada (https://inspection.canada.ca/plant-varieties/plants-with-novel-traits/applicants/pre-submission-consultation/eng/1368394145255/1368394206548#:~:text=A%20pre%2Dsubmission%20consultation%20is,submission%20is%20submitted%20for%20assessment).	Early

[5] This table provides examples of how a consultative process can inform a Safe(r) Innovation Approach. Engagements are voluntary, are not part of any regulatory obligations, and could take place in any order.

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
			Pre-notification consulations with Environment and Climate Change Canada and Health Canada during the planning or preparation of a notification of living organisms that are animate products of biotechnology subject to the *New Substances Notification Regulations (Organisms)* of the Canadian Environmental Protection Act (CEPA, 1999). https://www.canada.ca/en/environment-climate-change/services/managing-pollution/evaluating-new-substances/notification-forms.html#toc3 Prior Engagement Instance (PCI) in Argentina allows developers to submit a product (in the design phase or finished) to the autho rities to determine if it is covered by the GMO regulation (https://www.frontiersin.org/articles/10.3389/fbioe.2022.835378/full). US regulatory agencies engage in and promote such meetings b ecause they help create a more predictable regulatory pathway.	
Invited Expert Engagements, including end-user and stakeholder engagement (e.g. farmers, processing facilities, environmental stakeholder groups)	Consulting with subject matter experts to solicit their input on risk/safety associated with the use of a technology or product under development. This may be helpful to solicit input on risk/safety and ways they might be addressed or mitigated through product design and development. These engagements could be initiated by product developers or be initiated by regulatory authorities based on the need to formulate guidance or prepare for future risk/safety	When a technology is novel, but the intended use, environmental or human health exposures may not be familiar to a group of experts then it can be helpful to solicit input on risk/safety and ways they might be addressed or mitigated through product design and development.	US EPA's scientific advisory panel process is an example of an invited expert engagement	Early-Mid-Late

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
	assessment or possible post market management of anticipated technologies.			
Open Engagements; Including Experts	This is an engagement involving an open solicitation for expert opinion. The mechanism for accomplishing this engagement might be through a publication inviting comments from experts in the field or through a survey or other information collection system. Alternatively, an open meeting might be held where experts in the field register to participate in the engagement. In both cases, the engagement is typically guided by a set of parameters (e.g. guided questions) developed in advance to solicit information related to a specific set of risks or elements of a product design process.	When there are concerns whether plausible pathways to harm might have been previously overlooked, or to confirm that design elements address the earlier identified risks.	Most public commenting periods for regulatory decision making follow a kind of Open Expert Engagement model. In Canada, Environment and Climate Change Canada and Health Canada publishes summaries of certain New Substances Notifications (NSNs) submitted and invites stakeholders to provide comments, including scientific information and test data related to potential risks to the environment or human health from the new living organisms. https://www.canada.ca/en/environment-climate-change/services/managing-pollution/evaluating-new-substances/voluntary-public-engagement-initiative.html In the US, for example, the Environmental Protection Agency (EPA) has a public participation process for pesticides with new active ingredients, including those created through modern biotechnology (such as IR maize): https://www.epa.gov/pesticide-registration/public-participation-process-registration-actions.	Late-near final
Stakeholder workshop about emerging risks	A stakeholder workshop organised by researchers/developers to enable a constructive discussion about emerging risks with a broad range of stakeholders. A step-by-step approach can be used to identify uncertainties, develop anticipatory strategies and	When a responsible learning environment is needed to explore uncertainties.	Bouchaut et al (2022), Uncertainties and uncertain risks of emerging biotechnology applications: A social learning workshop for stakeholder communication. AFSI (2021), Expert Working Group on Harmonisation of Safety Assessment of Foods with members from Bangladesh, Bhutan, India, and Sri Lanka. (2021). CERA. (2013). Surrogate Species Selection for Assessing Potential Adverse Environmental Impacts of Genetically	Early-mid

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
	adaptations in (experimental) research designs to lower or mitigate identified uncertainties. It also helps to identify knowledge gaps for which (additional) risk research should be set up.		Engineered Plants on Non-Target Organisms Problem Formulation for the Environmental risk Assessment of RNAi Plants: Conference Proceedings https://foodsystems.org/wp-content/uploads/2021/02/pub_08_2011.pdf Problem formulation in Environmental Risk Assessment of Genetically Modified Crops: A Brazilian Workshop https://foodsystems.org/wp-content/uploads/2021/02/Problem-Formulation-pub_02_2009.pdf Storer NP et al (2024) Modernizing and harmonizing regulatory data requirements for genetically modified crops—perspectives from a workshop	
Technology specific or Product Ambiguity-resolving Engagements	Engagement with a broad consideration of a technology or use of a technology that are not intended to address a single, specific product under development. These may be convened by developers but also by regulatory authorities, scientific research organizations, NGOs or others to consider the risks that might be incorporated into product design for a variety of different products.	When a particular technology has multiple anticipated uses or when multiple known products are under development.	Consultative programs on Engineered Gene Drives in the EU (workshop in 2019?) ILSI Research Foundation Problem Formulation Workshop in RNAi technologies (2011) Participation in international, multi-stakeholder technical committees, coordinated by an independent, neutral organization, in a pre-competitive environment, to address broad safety considerations/approaches (not intended to address a single, specific product under development). Example: https://hesiglobal.org/protein-allergens-toxins-and-bioinformatics-committee-patb HESI Workshop – Safety assessment of newly expressed proteins in foods: need for evolution? October 21-22, 2024. Porto, Portugal. https://hesiglobal.org/event/hesi-workshop-safety-assessment-of-newly-expressed-proteins-in-foods-need-for-evolution/	Early

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
			HESI PATB Protein Toxins Workshop: From Protein Toxins to Applied Toxicological Testing. October 21-23, 2020. Online. https://hesiglobal.org/event/patb-committee-protein-toxins-workshop/. Workshop report: Bauman et al. 2022. Reg. Tox. Pharm. OECD Conference on RNAi based Pesticides April 10th-12th, 2019; Paris, France https://www.oecd.org/en/events/2019/04/conference-on-rnai-based-pesticides.html Summary of discussions: https://www.frontiersin.org/journals/plant-science/articles/10.3389/fpls.2020.00740/full HESI Workshop: Bioinformatics Approaches to Assess Safety of Novel Proteins in Relation to Food Hypersensitivity. Oct. 17-18, 2018. https://hesiglobal.org/event/bioinformatics-approaches-to-assess-safety-of-novel-proteins-in-relation-to-food-hypersensitivity/ HESI New Methods Workshop. October 23-25, 2007. Nice, France. https://hesiglobal.org/event/hesi-patc-new-methods-workshop/	
Localised problem identification engagement	Early discussions between regulators, developers and stakeholders within areas where the use of the technology is proposed.	When the technology is novel to better understand and address concerns local to where this technology may be utilised: is it the best or most sustainable solution? If so, why?	The public engagements on malaria described in section 4.2 of this document. Developers in the UK have been presenting the concept behind gene drive solutions for grey squirrel control to regulators and the public	Early
Regulatory experts engagement	Pre-submission discussions between regulatory risk assessment experts from different competent authorities	When there is a need to clarify the applicable regulatory pathway to market or development of a	Engagements on clarifying appropriate risk assessment approaches for gene drive organisms involving experts from European EPAs (environmental protection agencies) and ENCAs (nature conservation agencies) *	Mid-Late

Type of engagement	Brief description	When might this approach be useful?	Example of this type of engagement	Timing of the engagement relative to product development
		technology or product.		

* The engagement led to the publication of a number of documents:
(1) A technical report published by involved agencies in 2020 (GENE DRIVE ORGANISMS: Implications for the Environment and Nature Conservation. A joint technical report of the EPA/ENCA Interest Group on Risk Assessment and Monitoring of GMOs), https://www.bafu.admin.ch/bafu/de/home/themen/biotechnologie/fachinformationen/ig-gmo.html
(2) An opinion paper on impacts of Gene Drive Organisms on the Environment and Nature Conservation in 2021 (An Opinion Paper of the Joint EPA / ENCA Interest Group on GMO) https://www.bafu.admin.ch/bafu/de/home/themen/biotechnologie/fachinformationen/ig-gmo.html
(3) A scientific publication by experts involved in the engagement in 2020 (Dolezel M, Lüthi C, Gaugitsch H (2020), https://doi.org/10.3897/biorisk.15.49297)

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4 Illustrative examples

The two examples in section 4 were developed to illustrate how developers can apply design elements (set out in Table 1 in Section 3) and/or engagement considerations (detailed in Table 2 in Section 3), to support the development of safe products and obtain an easier pathway through the regulatory process. Both examples illustrate how (elements of) the concept of SIA may be deployed in practice. The purpose of this section 4, however, is not to give a comprehensive overview of the current scientific advancements nor a full overview of relevant SIA elements or to describe what information is needed to inform a regulatory risk/safety assessment.

The first example focuses on insect-resistant (IR) maize as a retrospective case study, illustrating how developers have used SIA elements even before the SIA concept had been formally articulated. Thus, the SIA elements were retrospectively identified as they were not deliberately considered in the frame of "SIA" at the time. Several IR maize and other crop products have since undergone regulatory assessment, obtained regulatory approval, and have been commercialised in several jurisdictions. The example of IR maize provides an illustration of how design considerations can be employed to minimise risks to the environment, and human health. Additionally, the IR maize example illustrates how collaboration with regulators on the use of the product post-regulatory approval can result in environmental benefits through the prolonged use of biotechnology products with a favourable risk profile.

The second example focuses on organisms containing engineered gene drives and showcases how developers are applying elements consistent with SIA in the R&D process for a type of product[6] that has not yet been released into the environment for testing or deployed on a large-scale. This example was selected due to the novel environmental considerations compared to genetically modified organisms released into the environment to date. Given the novelty, the gene drive research community is actively engaged in ongoing efforts in raising public awareness regarding the technology and in building a body of knowledge on aspects of risk/safety assessment, including how to apply a problem formulation approach and what would be considered a plausible pathway to harm. The example on engineered gene drives provides an opportunity to illustrate how technical design options may be employed to reduce risks to human health and the environment, and how engagement with government regulators, as well as public and stakeholder engagement can help identify pathways to harm that may warrant consideration.

4-1. Example of the Safe(r) Innovation Approach in IR maize

i. Overview of Insect-Resistant Maize & Risk Analysis Paradigm

In the mid-1990s, genetically modified insect-resistant (IR) maize was first commercialized in the United States, and currently, over 150 insect resistant maize products have since been approved in countries

[6] A final 'product' may not always be a commercial product but may be deployed for broader societal purpose, e.g. controlling malaria or invasive species.

around the world[7]. IR maize is a selective pest control technology with little to no confirmed negative consequences for non-target invertebrate populations, especially when compared with alternative pest control tools such as broad-spectrum insecticides (Meissle et al., 2022; Rose and Dively 2007; Sisterson et al., 2004; Truter et al. 2014). The addition of IR maize has led to the reduction in the use of insecticide applications and to an increase in crop yield (USDA 2014; Bertho et al., 2020).

Most commercially used insect resistant traits are developed by expression of insecticidal proteins derived from *Bacillus thuringiensis* (*Bt*). Bt is a naturally occurring soil bacterium that produces proteins active against specific insects and has been used as a safe microbial insecticide for over 50 years (Mendelsohn et al., 2003). For genetically modified organisms (GMOs), these bacterial toxins have often been synthetically engineered to increase efficacy against pest species, e. g. by combining domains of toxin classes to create new insecticidal toxins with the aim of improving target toxicity and delaying the evolution of resistance. These proteins tend to be highly specific in their insecticidal activity and often act through a pore-forming mechanism in the insect midgut. In recent years, insect resistant crop technology has expanded to include proteins derived from non-*Bt* microorganisms and ferns, as well as to other mechanisms of action like RNA interference. Regardless of the source organisms or mechanisms of action, considerations consistent with elements of SIA have played a role in the safe development of insect resistant crops, including maize, and are expected to continue to be applied and adapted as technologies evolve.

ii. Product Lifecycle Phase Considerations

SIA includes considering a product's entire lifecycle. As described earlier, IR maize represents a selective pest control technology with little to no confirmed negative consequences for non-target organism populations (He et al., 2025; Marvier et al., 2007; Meissle et al., 2022; Mendelsohn et al., 2003). Insects are constantly evolving, and if target pest insects develop resistance, the benefits of using these products may be eroded. As such, regulators and developers have worked to maintain the durability of these tools and to maintain effective use of these products to mitigate the development of resistance in target pests. In this way, the reduced use of broad-spectrum insecticides can be extended, consequentially leading to fewer sensitive species at risk when growing IR maize compared to using broad spectrum insecticides (US EPA 2001, 2010).

Several factors must be balanced against one another throughout all phases of product development, deployment, and maintenance to produce safe, efficacious, and durable technologies. Technical choices made during the design phase must balance factors that may compete with one another, such as agronomic trait performance, efficacy against the target pest, risk to non-target organisms, and product durability. These considerations extend beyond "safety" *per se*, with considerations of performance, efficacy and durability also of commercial interest.

Phase 1: Idea

IR maize has a history of safe use and successful commercialisation in markets such as the United States, Canada and Brazil. Despite this history, the development timeline for biotechnology crops is a multi-year endeavour. The time required to take a biotechnology crop[8] from gene discovery to commercialization is ~16 years with the discovery phase accounting for ~13%, and genetic event construction and testing accounting for ~36% of the total time (AgBioInvestor 2022). The regulatory assessment and registration along with breeding and trait introgression account for the remaining 51% of the development time. Given

[7] https://www.isaaa.org/gmapprovaldatabase/advsearch/default.asp?CropID=6&TraitTypeID=2&DeveloperID=Any&CountryID=Any&ApprovalTypeID=Any

[8] "Biotechnology crop" refers to crops containing transgenic traits that may present novel exposures. It does not refer to crops developed using new plant breeding techniques.

this lengthy development timeline, it is important for a developer to consider a product's lifecycle at the idea phase. One way this can be achieved is through the industry initiative of Excellence Through Stewardship (ETS) guides[9], which promote the adoption of product stewardship programs for the entire lifecycle of agricultural biotechnology products.

At the idea phase, developers identify a need for a trait (e.g., provide maize resistance to a target pest), the product's use (e.g., food/feed, non-food/feed), and a potential market (e.g., consumer/grower). In conjunction, developers also begin to consider the regulatory pathway. A commodity crop like maize requires consideration of relevant global regulatory frameworks prior to commercialization in countries where the crop is intended to be cultivated as well as the countries that import the resulting grain to avoid any trade disruptions. Therefore, an understanding of global regulatory frameworks and their requirements as well as timelines is necessary to successfully commercialize a product.

Phase 2 & 3: From Gene Discovery to Regulatory Submission- an iterative process of R&D and regulatory engagement

Successfully developing and commercializing a genetically engineered crop is an iterative and multi-year process. Various activities overlap but can be divided into the phases of gene discovery, trait validation, early development, and advanced development (see Prado et al. 2014). Below, we summarize how developers consider SIA throughout these stages of development and engagement.

Gene discovery & early regulatory considerations

At the early stages of development, developers test thousands of genes to identify the appropriate sources of genetic sequences for the trait of interest and design a genetic construct. Once these appropriate genetic sequences are identified, developers will perform literature searches and bioinformatics assessments to minimize the likelihood that the resulting proteins could trigger any food and feed safety concerns, such as allergenicity and toxicity. It is advantageous to a developer to perform preliminary *in silico* toxicity and allergenicity assessments of candidate genetic sequences before taking steps to express the protein in target plants. By performing these analyses early, their results can rule out sources or genes that are more likely to raise safety concerns or regulatory issues later. As such, developers routinely perform *in silico* and other safety analyses early in the product development process to have increased confidence that the product will be safe, which will also facilitate regulatory assessment and approval, contributing to consumer acceptance of the product.

Likewise, on the environmental risk assessment side, design choices are balanced by requirements to achieve necessary levels of target pest efficacy while minimising potential risk to non-target organisms. The specificity of the insect resistance trait typically limits concerns regarding non-target species, and design choices surrounding the trait expression profile can significantly reduce potential exposure to non-target organisms, e.g., by avoiding or minimizing expression in relevant tissues. Products are typically designed by considering how the biology and ecology of non-target organisms and the modified plant relate to exposure, e.g., how the plant is pollinated (wind pollinated maize) and how non-target organisms could interact with the modified plant (butterfly caterpillars eating larval host plant leaves with maize pollen grains on the surface). With this knowledge, developers attempt to design expression constructs to minimize exposure routes to non-target species (Liu, 2009). These considerations in product design can significantly limit the potential for non-target organism exposure and are generally consistent with the concept of SIA.

The concept of SIA also involves considering a product's entire lifecycle, and for IR maize, design choices that directly impact the longevity of the trait are considered early in the development process. For example, the durability of insect resistance traits can be improved using pyramided products. Resistance

[9] https://www.excellencethroughstewardship.org/ets-guides

management defines a pyramid as two or more controlling traits targeted at the same pest complex. Research and simulation modelling have shown that pyramided products can be more durable than single-trait varieties (Roush, 1998; Zhao et al., 2003; Gould et al., 2006; Onstad & Meinke, 2010), provided that the traits are expressed at high doses and have independent modes of action (i.e., low cross-resistance potential).

Product development for regulatory readiness & trait integration

The gene (e.g., *Bt*) that encodes for the insecticidal protein is first inserted into maize using genetic engineering, to create initial genetically modified (GM) events. These initial events are studied substantially by plant breeders who conduct thorough analysis that provides assurances on successful field performance such as trait efficacy, agronomic characteristics, yield, disease resistance stress tolerance, maturity, end use properties, if applicable (Moose & Mumm, 2008; Sharma et al. 2025). Events that do not perform to standards are discarded thus minimizing the possibility of negative health or environmental impacts. This process may start with 8000 to 12000 candidate plants, and only advance with 2 to 4 elite lines that may hold some promise as finished varieties (Prado et al. 2014) (Morrell et al. 2011). The extensive monitoring ensures stability and expression of the trait. They also serve as the underlying basis for regulatory applications.

In parallel to these studies, plant breeding is then used to cross the lead events into elite varieties to introgress the traits into elite germplasm of existing cultivating varieties for commercial release. Plant breeding is a highly developed field with rigorous established practices whose main objective is to improve elite breeding lines, without negatively impacting the performance gains that have been achieved over years of breeding and selection. To successfully introduce a new candidate trait, plant breeders need to have deep knowledge of the crop species and their genetics and monitor all aspects of new lines in each step of the breeding process. Specifically, breeders introduce the genetically engineered trait into elite germplasm, creating thousands of lines which are screened to ensure that only elite candidates that show the right phenotype are advanced These elite lines are then advanced to field trials where they are grown in diverse environments that evaluate agronomic performance and plant quality; underperforming varieties are discarded (Kaiser et al. 2020). It is important to highlight that trait introgression into commercially relevant germplasm is a separate process than the GM regulatory assessment and is related to the variety registration process for commercial release to ensure that the seed to be sold meets the claimed performance.

Trait validation & regulatory engagement

Preliminary safety assessments to confirm the specificity of the trait to the target taxa is an essential step in trait validation and to ensure the advantages of the product in terms of specificity and therefore in avoiding effects on non-target organisms. For example, when developing a new insect resistance trait in maize, laboratory screening tests are conducted to characterise insecticidal activity of the trait against the target species (e.g., OECD guidelines for toxicity testing). Further tests are typically performed to investigate the activity of the protein against species closely related to the target pest, as well as against other insect orders representing relevant functions in the ecosystem. Developers, and subsequently regulators, use the results of this testing and the specificity of the insect resistance trait to characterise the potential for risk to non-target organisms.

Developers will screen modified plants that produce levels of the insecticidal trait at sufficient levels and desired tissues to achieve optimal product efficacy and to avoid levels which could unnecessarily increase exposure to non-target organisms. This customised approach to product design further limits the potential for non-target organism exposure.

In terms of navigating the regulatory process, developers may engage regulators at this phase for an early concept meeting, particularly if they are developing a product in which regulators have less experience.

These meetings could allow developers to present data from the literature or their own early studies on safety and efficacy. Early concept meetings may also be useful as part of a regulatory strategy development as it can support creating awareness of any relevant changes in the regulatory landscape.

Early development & regulatory engagement

After selecting a few events for potential commercialisation, developers collect additional data on food and environmental safety. At this stage it is useful to engage in a pre-submission meeting with regulators. Here, regulators can clarify data needs and provide previous risk assessments (where available) that could guide further safety testing. For insect resistant maize, regulatory dossiers typically provide information relevant to the potential for risk to non-target organisms and food safety.

In general, the potential for risk to non-target species populations, communities, and the ecosystem combines information on the expected exposure along with scientific rationale and toxicity testing from various functional groups. Information from initial activity spectrum studies inform taxa selection for subsequent laboratory testing of beneficial non-target organisms that represent vital ecosystem functions to determine potentially sensitive taxa. Aside from determining hazard, expected exposure is characterised by assessing expression levels of the trait across multiple tissues and life stages of the plant, degradation patterns, and basic information on the crop itself, including biology, ecology, flower phenology, and the taxonomy of the species and its relatives (Kough & Edelstein, 2013). To ensure broad data coverage, the studies are often conducted in multiple cultivation testing sites. Information collected on hazard and exposure is then analysed together to determine potential risk to non-target organisms. Mathematical models may also aid risk characterization of IR maize for non-target organisms, such as lepidopterans (EFSA, 2015; Hoffman et al., 2016).

The food and feed safety considerations of the insecticidal trait utilises a robust weight-of-evidence approach based on a combination of *in silico*, *in vitro*, and *in vivo* animal data to demonstrate that the protein is not structurally related to any known mammalian toxins or food allergens, that it generally behaves as would be expected of a dietary protein (i.e., it is digested in the gastrointestinal tract), and that it is not toxic at levels well above the exposure levels that are reasonably anticipated to occur through the dietary consumption of the crop. Although there are currently no definitive tests for determining the allergenic potential of novel proteins, the Annex to the Codex Alimentarius “Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants” provides a weight-of-evidence approach for this type of assessment. Codex considers the following factors: trait source, amino acid sequence comparison with known allergens, and biochemical properties of the protein, including *in vitro* digestibility in simulated gastric fluid containing pepsin and glycosylation status of the plant-expressed protein. In addition to investigating the insecticidal trait itself, developers and regulators have considered whether human and animal foods produced from insect resistant varieties were meaningfully different in levels of key nutrients, anti-nutrients and toxicants.[10] These analyses helped developers and regulators

[10] See for example: Comparison of the Forage and Grain Composition from Insect-Protected and Glyphosate-Tolerant MON 88017 Corn to Conventional Corn (Zea mays L.) Melinda C. McCann, William A. Trujillo, Susan G. Riordan, Roy Sorbet, Natalia N. Bogdanova, and Ravinder S. Sidhu Journal of Agricultural and Food Chemistry 2007 55 (10), 4034-4042 DOI: 10.1021/jf063499a, Compositional Equivalency of Cry1F Corn Event TC6275 and Conventional Corn (Zea mays L.); Rod A. Herman, Amy M. Phillips, Randy A. Collins, Laura A. Tagliani, Fred A. Claussen, Christopher D. Graham, Brenda L. Bickers, Travis A. Harris, and Lee M. Prochaska Journal of Agricultural and Food Chemistry 2004 52 (9), 2726-2734 DOI: 10.1021/jf049969n; Composition of Grain and Forage from Corn Rootworm-Protected Corn Event MON 863 Is Equivalent to That of Conventional Corn (Zea mays L.); Cherian George, William P. Ridley, Janet C. Obert, Margaret A. Nemeth, Matthew L. Breeze, and James D. Astwood Journal of Agricultural and Food Chemistry 2004 52 (13), 4149-4158 DOI: 10.1021/jf035023m; Comparison of the Forage and Grain Composition from Insect-Protected and Glyphosate-Tolerant MON 88017 Corn to Conventional Corn (Zea mays L.) Melinda C. McCann, William A. Trujillo, Susan G. Riordan, Roy Sorbet, Natalia N. Bogdanova, and Ravinder S. Sidhu Journal of Agricultural and Food Chemistry 2007 55 (10), 4034-4042 DOI: 10.1021/jf063499a; Composition of Forage and Grain from Second-Generation Insect-Protected Corn MON 89034 Is Equivalent to That of Conventional Corn (Zea mays L.) Suzanne M. Drury, Tracey L. Reynolds, William P. Ridley,

determine that products from insect resistant maize would be as safe as similar corn products when used in human and animal food (see for example Herman et al., 2007).

Advanced development & regulatory submissions and reviews

At this stage, developers will have a successful lead event characterised that has performed well during development testing and is deemed safe and durable. With the global regulatory data package in-hand, developers will start to apply for relevant regulatory approvals to ultimately enable the commercialisation of the event in the relevant geographies, which includes intended cultivation markets and potential import markets of the harvested grain . The application package for distinct countries and agencies may have different components yet include core commonalities (e.g., testing methodology, scientific rationales). Ongoing conversations between regulators and developers can occur if any further information or data are needed during the regulatory review processes[11]. Regulatory approvals also serve the purpose of enabling farmers to sell their grain in global markets.

To maximise the durability of their crop, developers of insect resistant crops have an interest in developing a resistance management strategy. This is a commercial interest that is compatible with optimizing environmental benefits. In some countries like Canada and the United States, regulatory agencies require developers to address the product lifecycle of insect resistant technology. In other jurisdictions, industry-developed standards may apply. One of the avenues to achieving this is through a resistance management plan, which aims to prevent and delay the development of resistance in the target insects. These plans may be part of the dossier submitted for a safety assessment (CFIA 2014, 2017) and describe how the technology will be managed or under what conditions it will be used. These plans may include information about the biology of the insect pest (e.g., European corn borer, corn rootworm), the mobility of the larvae, the impact of management practices, the history of insect resistance to active compounds, and provide education to stakeholders, communication mechanisms with growers among others.[12]

Phase 4: Product Launch

After an insect resistant maize product has received all the relevant regulatory approvals, SIA considerations may continue to apply until product discontinuation through post-market activities. Examples of these activities are, implementation of insect resistance management plans, case specific monitoring, or general surveillance, if applicable. The primary resistance management strategy for insect resistant maize has been using non-resistant insect refuges, which serve as sources of susceptible target insects that mate with resistant individuals emerging from insect resistant maize fields. The goal of this strategy is ultimately to reduce the frequency of resistance genes in the overall pest population. Refuge size and structure are determined by the biology and ecology of the targeted pests and the effective dose of the insect resistant crop against these pests while accounting for the grower's needs for practical implementation. Successful insect resistance management requires engagement with the grower community to ensure that the importance and logistics of the strategies are understood and implemented.

Natalia Bogdanova, Susan Riordan, Margaret A. Nemeth, Roy Sorbet, William A. Trujillo, and Matthew L. Breeze Journal of Agricultural and Food Chemistry 2008 56 (12), 4623-4630 DOI: 10.1021/jf800011u; The Forage and Grain of MON 87460, a Drought-Tolerant Corn Hybrid, Are Compositionally Equivalent to That of Conventional Corn George G. Harrigan, William P. Ridley, Kathleen D. Miller, Roy Sorbet, Susan G. Riordan, Margaret A. Nemeth, William Reeves, and Todd A. Pester Journal of Agricultural and Food Chemistry 2009 57 (20), 9754-9763 DOI: 10.1021/jf9021515

[11] The OECD Consensus Document on the Biology of Maize and the Consensus Document on Compositional Considerations for New Varieties of Maize (OECD 2006; OECD 2015) provide information to help define the baseline and scope of the risk/safety assessment.

[12] A list of the elements IRM plans should address in Canada is available at the CFIA website (CFIA 2017) and a list for the United States is available at the EPA website (US EPA 2021).

In several countries where IR maize is being grown, such as Canada[13] and the United States[14], coalitions and committees work to develop research, stewardship, and educational programs that promote the responsible use of insect resistant maize products to promote durability and longevity for all stakeholders[15]. Additionally, industry initiatives such as Excellence Through Stewardship (ETS) have developed guides[16], which promote the adoption of product stewardship programs for the entire lifecycle of agriculture biotechnology products from launch to discontinuation, and these have been utilised by developers in the development and commercialisation of biotechnology products.

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4-2. Example of the Safe(r) Innovation approach in engineered gene drives

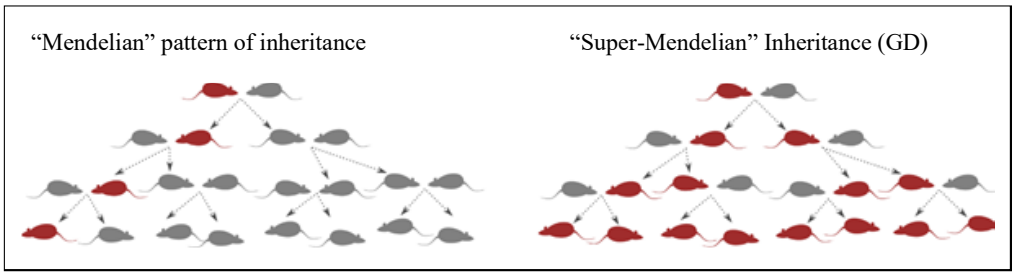
i. Introduction

Genetically modified organisms (GMOs) containing 'engineered gene drives' (EGDs. EGD-GMOs) have not yet been deployed in the environment, however there is active research on their design(s) and potential application. As such, these organisms provide a pertinent, 'real world' example of how elements consistent with the SIA concept can be considered, implemented and communicated in the nascent stages of a technology.

EGDs are genetic constructs designed to bias the inheritance of a particular gene and 'drive' that gene to high frequency in a wild population. The concept of an EGD was inspired by naturally occurring 'selfish genes' or 'selfish genetic elements', some known since the early 1900s, that are inherited by more offspring than expected under Mendelian inheritance (Werren, 2011). Molecular adaptation of naturally occurring 'selfish genetic elements' was proposed as a tool for increasing the frequency of a desired genetic trait in populations in the environment (Burt, 2003). With the advent of modern genome editing tools, such as the CRISPR-Cas system, the construction of such EGDs became much more technically feasible (Bier, 2022). Mating of GMOs containing an EGD (EGD-GMOs) in a wild population would be expected to result in 'Super-Mendelian' inheritance of the EGD in progeny and subsequent generations (see Figure 3), with the EGD and any linked trait theoretically penetrating the whole population.

The most commonly proposed applications of EGD-GMOs include disease control (e.g., reduce malaria and improve human health through control of the Anopheline mosquito vector) and invasive species/pest control (e.g., protect island biodiversity through invasive rodent control) (Bier, 2022). Recently, EGDs were designed to change the composition of virus populations in order to increase the frequency of variants which are less pathogenic for human or mammalian hosts (Walter and Verdin, 2020). While such "viral GDs" use a similar drive mechanism as employed in other EGDs, the drive is not spread by sexual reproduction, but rather upon co-infection of host cells by wildtype viruses and viruses modified with GDs (Walter et al., 2024).

Figure 3. Schematic representation of Mendelian (non-gene drive) vs Super-Mendelian (gene drive) inheritance patterns of a trait in a mating population



With permission from: Umweltbundesamt/I. Offenthaler

Several applications of EGD-GMOs have been proposed and they can be broadly grouped into two categories. The first is population suppression, where a trait is introduced that reduces the population of the targeted[17] species below the level needed to persist or to vector disease. The second is population

[17] In this document targeted species is used as a shorthand to denote the species/population into which an EGD might be introduced, the 'recipient species', and does not necessarily imply 'target' in the sense used in the context of pesticides - 'target organisms'

modification, where a trait is introduced that alters the targeted species in a desirable way (e.g. reducing the ability to vector disease, provides a survival advantage for an endangered species).

EGDs are in various stages of development, and the R&D community has consulted widely, for example with regulatory and scientific experts, and engaged with communities in the areas of proposed deployment of the technology.

The use of consultations with regulators, researchers, and the public is consistent with the concept of SIA in two ways. First, it assists product developers in understanding how regulators identify and assess risks. Second, it allows developers to hear from external and local experts and local communities and helps to identify any specific pathways to harm and/or relevant characteristics of the wild population and receiving environment (including for example, local environmental values) that may not have been considered during the research and development process.

ii. Lifecycle Phase Considerations

SIA includes considering safety and engagement throughout a product's entire lifecycle: the idea phase, research & development phase, regulatory process phase, and post product launch phase. As EGDs have not yet been deployed in the environment, the technology has not undergone all the phases in a product lifecycle. However, as discussed below, SIA concepts have been exemplified in the first two phases. In relation to SIA, it is important to note that a variety of different designs and applications of EGDs are possible. Thus, the aim of this example is to outline considerations and options that may be used in the development of EGD organisms to inform choices in the technical design phase. This document does not serve as a guide to risk/safety assessment criteria proposed by any OECD member country; therefore, it does not address the risk/safety assessment of gene drive products.

Phases 1 & 2: From Idea to Product Prototype- an iterative process of R&D and engagement

Design Considerations

Design considerations for EGDs are informed by technological capacity, the proposed use and the potential receiving environments, consultations with regulators, and in some cases, with the community where the technology is intended to be deployed. The extent and utility of such consultations will vary depending on the jurisdiction, the nature of the EGD, EGD-GMOs under discussion, and local laws and procedures governing interactions between regulators and developers. In cases like EGDs, where the technology and the proposed use are novel, and experience on practical risk assessment is limited, more consultative efforts may be justified to promote a common understanding between developers, regulators, and the research community (and ultimately the public) of what would be a harm and how risk/safety assessment would be accomplished. When the technology applied or application itself has novel properties and/or has not yet been released, such as with EGDs, consultative efforts may be generally useful. On the other hand, when the organism being considered more closely resembles genetically engineered organisms that have previously been subject to risk/safety assessment, or for which there is significant prior experience in the environment, then broad consultative efforts or engagements may not be as useful. Leveraging previous experience and existing information from interventions with similar intended outcomes may also aid engagement efforts. Relevant examples in this context would be the introduction/release of biocontrol agents and releases intended to skew the population of pests via mating outcomes, e.g. ‘sterile males’ (SIT = sterile insect technique), introgression of *Wolbachia* strains into mosquito populations to suppress dengue virus, genetically modified insects designed to bias sex ratios, and biocontrol of invasive alien species.

There are many relevant design considerations, including a variety of molecular and other technical options consistent with a SIA approach, for the design of an EGD, an EGD organism, and experimentation and/or

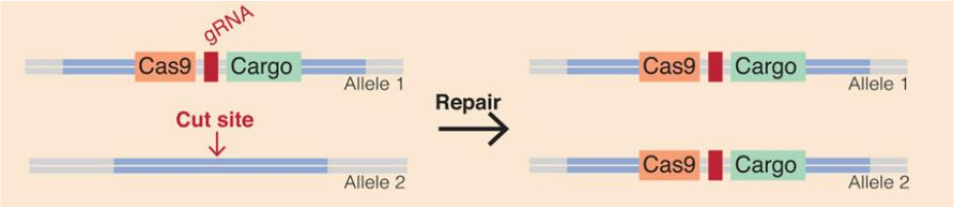
deployment (See also Table 3 below). Elements of SIA may support such considerations, inform options at each stage, and influence each subsequent step in a development and (possibly) deployment pathway. Decisions made at all stages of development influence the range of possible outcomes from use of an EGD. Considering options at all stages may help to make informed decisions to limit the potential for adverse effects and to determine data requirements. These considerations do not constitute recipes for design but rather highlight a range of issues that could be considered to inform choices throughout all phases from concept to development, regulation, and deployment.

Molecular considerations

The molecular design of an EGD comprises two elements: (1) the drive mechanism, which leads to super Mendelian inheritance, and (2) the gene(s) to be spread in the population – the EGD 'cargo'.

One example of a gene drive mechanism is "homing gene drives," which uses a site specific nuclease (such as Cas9 and a guide RNA) which determines with high specificity the genomic locus where the EGD construct is to be inserted (Burt, 2003; Simon et al., 2018; Pescod et al., 2024). Once a cut is made, homology directed repair will copy the EGD construct into the corresponding chromosome. Thus, when the fusion of gametes occurs after mating between an EGD-GMO and a wild type organism, the EGD construct will be copied and the resultant progeny will be homozygous for the EGD allele (see Figure 4). However, there are also other gene drive mechanisms that work very differently, and the nature and characteristics of the chosen drive components are an important consideration for safety throughout the development and (hypothetically) use of any gene drive organism.

Figure 4. Schematic of gene cutting and repair



Source: Marius Walter (https://commons.wikimedia.org/wiki/File:Gene_Drive.png), CC BY-SA 4.0

The step-by-step approach (OECD 1993) is relevant for the development of EGD applications: pre-experimental design and modelling of spread of an EGD in a population under different scenarios; appropriate physical containment at laboratory research stages; appropriate physical and/or biological confinement at field trial stages as available (WHO, 2021; Lanzaro et al., 2021). A modular design approach can facilitate testing of the different components of an EGD application, i.e. the drive system and the cargo, in separate parallel trials. The tested modules would then be combined at a later stage into a fully functional EGD based on accumulated risk/safety assessment data.

Examples for incorporating biological and environmental considerations in molecular design

The OECD concept of interaction of the biology of the parent organism, the introduced trait and the receiving environment is clearly applicable to both design choices and the later stage assessment of EGD organisms. Different designs, for example, may create EGD-GMOs with very different characteristics with respect to range, speed and longevity of spread on the one hand and environmental impacts on the other hand. The reproductive biology of the organism would be an important determinant of the rate of spread of an EGD (e.g. time to sexual maturity, numbers of progeny) and modelling may provide important information about population dynamics of an EGD. For this reason, gene drive developers have put significant consideration into the development of "product profiles," which are descriptions of what the drive

is intended to accomplish and the characteristics that are relevant for safety and effectiveness based on the intended purpose of the EGD (James et al., 2020; Mondal et al., 2025). These profiles can be modified over time based on feedback from new knowledge and from consultations with regulators and other stakeholders and represent a focus on safety during early design phases.

These considerations should address the specific characteristics of EGDs that make them distinct from most other types of GMO applications to date:

- Genetic modification events initiated by the gene drive would take place outside the laboratory (i.e. mating of a EGD-GMO with a wild type organism results in the EGD modifying the corresponding locus in the wild type chromosome in the zygote)
- The species proposed for EGD applications are mostly wild species in natural environments
- There may be limits to anticipatory risk assessment, due to a number of factors (e.g., risk issues associated with EGD components or introduced traits, the organisms targeted and its environmental interactions and the possibility for delayed effects to arise)
- There may be limits to a step by step approach due to practical limitations for containment/confinement, control and/or recovery of released EGD organisms, e.g. at increasing scale of field trials
- If wider geographical spread is intended or unavoidable, the ramifications of spread of EGD-GMOs across national borders would need to be considered

Molecular design to control the spread of EGD

One area of focus for molecular design of EGDs has been the temporal/spatial and population genetics relevant for an intended application, considering how quickly and how widely the EGD is intended to spread and looking at molecular mechanisms that can alter the expected ability of a drive to spread and persist. EGDs that can (theoretically) spread through an entire population with the release of a single individual EGD-GMO and would be expected to spread through any population where they are introduced have been referred to as “low threshold” drives. Safety considerations around the ability to control the spread of EGDs to affect target populations, but reduce the likelihood of spread outside target populations has produced a variety of proposals for “high threshold drives,” or drives that require a significant portion of a population to possess the EGD before the super Mendelian inheritance occurs (Barrett et al., 2019; Leftwich et al., 2018). Another self-limiting design that has been proposed for EGDs is the use of so-called ‘split drives’ that separate the operative elements of the drive in the genome. This increases the flexibility to update the EGD to target other genetic loci and to construct less invasive forms of drive that may be suitable to more localised applications.

Other theoretical design choices related to limiting the spread of an EGD include selection of specific insertion sites and choices on sex-biased inheritance patterns (male vs female inheritance). For example, the selection of the locus in the genome for insertion of the EGD is an important molecular consideration which can provide species and locus specificity and might be used to confine a EGD to specific sub-populations (the sequence of the guide RNA in the EGD construct directs Cas9 to this locus). Such designs would lower the possibility that the accidental introduction of a few modified individuals into geographically distant populations may start undesired further spreading. Alternatively, distorting sex ratios may also be considered as a population suppression strategy (X shredder, *Sry* gene in mice) (Leitschuh et al., 2018; Bier, 2022).

Removal and reversal considerations

Depending on the proposed use, the built-in ability to remove GMOs containing EGDs from the environment, including the ability for complete recovery or removal of the EGD-GMOs, may also be a consideration in the choice of a specific EGD design. Various options have been considered ranging from

release of individuals with a synthetic allele of the targeted gene that is resistant to the EGD, to release of a second EGD organism containing an “overwriting” or “reversal drive” (Vella et al. 2017).

While none of these design strategies have (to this point) been built into a functional gene drive that has been released into the environment, they reflect an awareness of safety during the early stages of molecular design and development and provide examples of how gene drive developers are implementing SIA.

Table 3. Choices for potential design, development and release of EGDs and GD organisms

Design considerations	Intent	Consideration and outcome
Context of proposed use	For pest species, consider the current controls being used, how would use of EGDs fit within the current control strategies? How might EGDs complement and/or replace some aspects. For valued species or populations[18], consider the requirements for protection and how use of EGDs may complement these.	EGDs form part of an integrated management strategy for pest species. Providing EGDs that complement established safe and effective controls and/or potentially replace less effective or less safe controls (e.g. use of certain chemical controls). For valued species or populations, providing EGDs that complement requirements for thriving or remove threats.
Consultation	Considering who could and should be consulted at each stage in the development of a EGD, about what, why, and when they should be consulted.	Input from and engagement with stakeholders can provide insights that inform design/development choices. Building knowledge of technical aspects, addressing concerns, understanding how decisions made at each stage may inform options for development/deployment.
Goal aspects	Defining and clarifying the desired outcome to design a drive to achieve that result while minimising off-target effects.	Informs precise design of drives, examines other considerations (population dynamics, ecology of the geographic area, the biology of the species of interest and related species) relevant to designing EGDs. Informs strategies for experimental work and release to maximise efficacy and effectiveness while minimising risk.
Biological considerations		
Species/populations of interest	Understanding of the biology, genetics, mating systems, mating preferences, population dynamics and ecology of the species of interest and of relevant related species[19]. Is the sequence of interest present in the species as a whole, or only in particular sub-population(s)? Understand the significance of release sites (receiving environment).	Informs options for the design of EGDs and release strategies to optimise specificity, efficacy and effectiveness of the release, including intended limits on the release, by identifying key factors within the population(s) of interest and release sites.
Status of species/populations	Knowledge of ecosystem function of the species of interest. Understanding whether a species of interest is universally regarded as a pest or a valuable species (depending on the intended use of the EGD).	Informs options for the design of EGDs and release strategies to minimise the risk that an organism which is a pest in one location/situation, but a valued species in another, is not universally affected in both. Or vice versa, depending on the intended use of the EGD.
Spatial Aspects		

[18] For some species the paradoxical situation exists that they are pests in one place and valued and/or endangered species in another part of the world, e.g. wild rabbits in Australia vs. Spain.
[19] The OECD Consensus Document on the Biology of Mosquito *Aedes aegypti* (OECD 2018) provides the information that could be commonly used in countries for risk/safety assessment. Consensus documents on the biology of mosquitoes *Anopheles gambiae*, *Anopheles albimanus* and *Anopheles stephensi* are under development.

Design considerations	Intent	Consideration and outcome
Physical containment	Containment options for research on EGD organisms in physical containment facilities at a level (e.g. PC / BCL 1-4) and type appropriate to the species (e.g. insectary, animal house, aquarium, or glasshouse) and the stage of development.	Prevents unauthorised release into the environment, while allowing work to proceed, to provide data and knowledge to inform choices further along the design, development, release and regulatory pathway.
Physical confinement	Physical separation of species or populations of interest and EGDs acting on these, from other populations within the species or related species where this is feasible.	Minimises the likelihood of EGDs spreading outside the population of interest or to related species and the risks to these populations. At early stages may allow to work on informing the design, while minimising risk.
Geographic isolation	Consideration of geographic separation of target populations within a species from other populations of the same species and if appropriate, from related species.	Minimises the likelihood of EGDs spreading outside the population of interest to other populations or to related species. Mitigates risk of spread from containment during research stages. May complement physical removal options (see below).
Combined geographic isolation, climatic limitations and containment	Conducting experimental work in a geographic location where the species of interest could not survive should it escape containment. Such locations are highly unlikely to have populations of the species or related species to which the EGD could spread.	Combination of factors designed to ensure that should physical containment be breached; geographic and climatic factors would minimise the likelihood of survival and spread to wild populations or related species.
Temporal aspects	Understanding how long a EGD would take to work in a mating population to achieve the desired effect – rate of spread, number of generations, generation time.	Informs the design of self-limiting or reversible drives, understanding of ecological impacts and whether these may be affected by speed of spread of the drive and resultant changes to population of interest, as applicable. Could assist in determining how long a drive would need to be active in a wild population to achieve the desired outcome, with minimal impact on the larger environment.
Modelling	Developing models to consider the influence of relevant factors such as those above, on the outcome of any release. Enables consideration of 'desk-top scenarios and how individual elements, or combinations of these, may contribute to different outcomes.	Informs EGD development and release strategies by exploring likely outcomes for a range of options, providing valuable information about the feasibility, efficacy and effectiveness, as well as risks, of various approaches before experimental work commences. Identifying key control points and areas if uncertainty.
Design of drive		
Self-limiting drives	E.g. split drives, daisy chain drives, high threshold "local" drives with the purpose to creating specific conditions for the EGD to work, separating elements of the drive from one another to promote greater control of and/or a finite life of the EGD.	The drive is not active at the release site indefinitely, or is maintained at low levels, thus limiting unintended effects and reducing likelihood and/or frequency of spread outside the population of interest.
Male or female inheritance	Meiotic drives to distort sex ratios in a population resulting population crash – population suppression (X shredder, *Sry* gene in mice).	EGD dies out with the crash of the population.
Site of insertion specificity	High specificity of activity of the drive.	Activity of the EGD outside the population or area of interest is highly unlikely.
Reversible drives	Development of a primary drive, to drive required change into a	The altered phenotype does not persist at high levels indefinitely after release. The

Design considerations	Intent	Consideration and outcome
	population, concurrently with development of a reverse/rescue drive that can be released at a defined point after the release of the primary drive resulting in reversion of phenotype (although not exact genotype).	reverse drive acts only on the individuals containing the initial drive elements, thus limiting its activity to those individuals.
Engineered safeguards and other controls		
Auxotrophy	Organism relies on the provision of a specific compound for growth and/or survival.	Organism can only survive in an environment where that compound is available/provided, most likely, in a laboratory. Management tool preventing inadvertent release from containment, particularly at early stages of development.
Systems requiring inducers/suppressor effectors	EGD(s) that would only work in the presence of a supplied inducer or can be 'disabled' by presence of a supplied suppressor.	Effectors can be used to control the activity of the drive either through inducing or suppressing activity. Use of drives in situations where the effector is not available unless supplied, or in an area where suppressors can be supplied, thus enabling control of activity.
Physical or biochemical characteristics	Ensuring the EGD and the organisms containing it are susceptible to removal and/or recovery	All organisms containing the EGD can be recovered, if required.

iii. Case Studies of the Iterative Process of R&D and Engagement

Many developers of EGDs have already begun engaging regulators and the public. With such engagement, developers can identify perceived or potential hazards and plausible pathways to harm and areas where research efforts could inform future risk/safety assessments. Concurrently, such engagements help build trust and foster mutual understandings of complex science (NAS 2016).

The two case studies below illustrate how EGDs can or have already incorporated aspects of engaging with regulators and the public into research and development. Regarding local community outreach, the two examples represent different challenges. One example contemplates community engagement occurring on a continent-wide scale while the other example localises community engagement to a small island town.

Malaria disease control in the African Union

Malaria is a devastating disease caused by a family of parasites with a complicated reproductive lifecycle involving both human hosts as well as specific species of Anopheles mosquitos. The most lethal of these is *Plasmodium falciparum* which continues to impact countries in Sub Saharan Africa. Intensive control efforts, including a major push for eradication at the start of the 21st century, have achieved significant success but are not likely resulting in the eradication of malaria. Coupled with the diminishing effectiveness of chemical pesticides, this has led to interest in exploring genetic technologies that might be effective in coordinated control programs to eliminate malaria transmission. EGDs are under consideration as tool to support disease control of malaria via control of the mosquito vector itself.

In this vein, discussions between regulatory officials, scientists, and developers to consider a gene drive approach to malaria eradication are important. The New Partnership for African Development, (supported by African and international partners including funders of malaria eradication research) held a series of workshops convened regionally in Eastern, Southern, Central and Western Africa. These workshops facilitated discussions between scientists and regulators. It provided an opportunity to review the underlying technology, the biology on Anopheline vectors of malaria, and how future risk/safety assessments might be conducted. This problem formulation approach encouraged participants to identify both broad and specific protection goals related to the environment and human health. It also encouraged stakeholders to consider how the introduction of an Anopheline mosquito carrying a gene drive construct might lead to the harm of an identified protection goal. The workshop also afforded an opportunity to researchers developing EGDs to learn from scientists and regulators about how they define risk and harm, how they would structure a risk/safety assessment, and what they would expect to be required for an application for an environmental release of gene drive mosquitoes to be appropriately assessed.

In addition to conversations between scientists and regulators, stakeholders have identified a need to structure engagement efforts to reflect country-specific governance based on their protection goals, and to incorporate community perspectives into research and development (Finda et al. 2023). Malaria impacts countries across the African Union differently and as such, the risk to benefit ratio of EGDs may differ by country. An EGD developer, Target Malaria, has initiated country-specific engagement through an ethnographic study to obtain an understanding of social and governance structures. This has allowed Target Malaria to listen to concerns from distinct stakeholders and acknowledge differences in values, with the goal of engaging and sharing evidence-based information (Pare Toe et al. 2022). Design considerations that incorporate public engagement could consider a variety of tools such as self-limiting drives, depending on if the primary goal is to spread a drive or localise it to a given region. Incorporating engagement with communities can facilitate the creation of a more community accepted technology.

Invasive pest control on islands

Islands are known for their high endemism levels and species richness, contributing 15-20% of terrestrial species. Yet pests and invasives threaten island biodiversity. In fact, over half of terrestrial extinctions since the 1500s have occurred on islands. Today, ~37% of island species are at risk of extinction (Tershy et al. 2015). One of the major threats they face are invasive pests and species such as invasive rodents, mosquitos, or ticks. To protect island biodiversity, biologists have searched for innovative tools such as EGDs. For example, the development of EGDs in rodents is being explored as a safer alternative to rodenticides which are known to have downstream effects on the ecosystem (Erofeeva et al. 2022).

Engagement with regulators about rodent gene drives on islands have happened in parallel to the research to inform the development of drive systems. Two groups, Genetic Biocontrol for Invasive Rodents (GBird) and Mice Against Ticks, have led various stakeholder workshops and focus groups (Godwin et al 2019). The “Exploring Stakeholder Perspectives on the Development of a Gene Drive Mouse for Biodiversity Protection” workshop held at North Carolina State University, gathered a diverse group of regulators, scientists, funders, and workshop leaders to discuss the development of a gene drive mouse for restoring biodiversity on islands (Farooque et al. 2019). This workshop provided an opportunity to review gene drive science and allowed stakeholders a platform to voice concerns on efficacy, safety, and durability. It also provided an opportunity to discuss the selection of potential candidate islands for field trials. By organising the workshop around different lifecycle phases of EGD development, stakeholders were able to discuss current, short-term, and long-term research.

Public engagement with people living on islands of proposed EGD rodent releases have also been conducted. For example, on the island town of Nantucket, public engagement is being led by Mice Against Ticks. Here, developers asked the community if they would be interested in the release of an EGD mouse to control tick-borne Lyme disease. The community was receptive, on the one condition that the introduced gene had to originate in the wild mouse population (*Peromyscus*). The team subsequently used this suggestion to lead their research efforts to isolate *Peromyscus* antibodies, despite the species being notoriously difficult to engineer (Buchthal et al. 2019; 2023). Other engagements are ongoing regarding different islands, such as some in New Zealand. These various engagements demonstrate the SIA element of incorporating diverse viewpoints and public concerns into innovation processes.

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