Policy Recommendations for the Regulation of Engineered Microbes for Environmental Release

June 2024

LCSSP The Ronald and Maxine Linde Center for Science, Society, and Policy

Caltech

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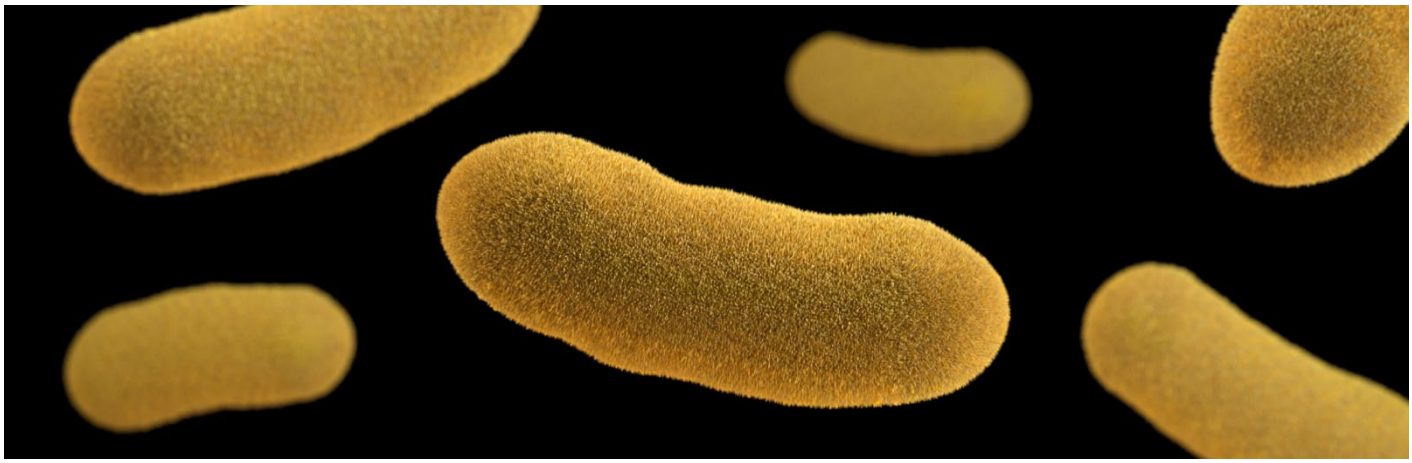

This document is a report authored by Caltech's Linde Center for Science, Society, and Policy (LCSSP) regarding regulations governing the environmental release of engineered microbial products. This document, and the recommendations in Chapter 7, were developed through initial discussions and subsequent feedback related to the "Pathways Towards the Safe and Effective Deployment of Engineered Microbial Technologies" Workshop hosted by the Linde Center for Science, Society, and Policy and Caltech's Resnick Sustainability Institute in February 2024.

As this document is not a consensus report, it should not be assumed that any particular workshop participant has endorsed any particular point made in the document. The document also contains brief, boxed sections authored by specific workshop participants to present additional perspectives on areas outside of the main scope of this report.

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Executive Summary

Engineered Microbes for Environmental Release (EMERs) are an emerging biotechnology sector that is poised to play a significant role in the global bioeconomy through their ability to address challenges related to climate change, environmental remediation and diagnostics, self-regenerating structural infrastructure, and more. However, the current U.S. regulatory system is not well equipped to efficiently regulate EMERs, leading to a large burden on EMER developers that may not be commensurate with the level of risk associated with the product. Such burdens impede innovation in the EMER sector.

We identify the major challenges with EMER regulation as:

1. EMERs are an emerging class of products that contain living engineered microbes that may not fit neatly within existing regulatory frameworks developed for more conventional products such as pesticides, drugs, agricultural chemicals, and food sources. As such, many **EMERs can fall outside the existing jurisdictional boundaries of regulatory agencies,** either via overlapping authorities or by falling within "regulatory gaps" that do not meet the typical remit of any single administrative unit. Resolving these issues adds significant complexity, time, and costs for both developers and regulators to the development and legal deployment of EMERs.

2. The **scientific knowledge base for EMERs, the microbes from which they are created, and their interactions and impacts on different natural environments is still underdeveloped.** Fundamental properties of microbial persistence and dispersal in various types of environments are still an active area of research, let alone the nature of ecosystem impacts when microbes are introduced into nonnative environments and whether/how any of these properties are affected by engineered modifications to the microbe. Understanding more about these interactions would enable a more science-based assessment of hazards, exposure routes, and attendant risks associated with the usage of EMERS, rather than requiring the current conservative assumptions that result from the need to be protective in the absence of scientific certainty.

3. Many of the **regulatory triggers for biotechnology products are not well aligned with the nature of EMERS and their likely uses.** Given the relative lack of scientific knowledge as described in (2) above, risk/safety assessments performed according to existing regulations and other regulatory instruments may employ outdated or inappropriate assessment methodologies and result in overly conservative, lengthy, and ultimately innovation-hampering regulation. Further, if there is no regulatory instrument appropriate for the regulation of EMERs they may not be regulated at all, and thus pose real health and environmental risks, as well as risking the public's trust in the ability of the federal government to adequately regulate biotechnology products.

Successfully addressing the regulatory challenges for emerging EMER products should be one of the key components in the ongoing U.S. efforts to advance the bioeconomy. In contrast, failing to address these challenges at this critical phase in the development of this biotechnology sector will continue to hamper U.S. interests via a loss of economic competitiveness and the potential for brain drain to other markets with regulatory systems that are more developed in meeting the needs of EMER regulation.

Our recommendations to address these challenges (Chapter 7) include the following:

A. Congress should establish and fully fund **a federal office to guide and support small / first-time EMER developers through the regulatory framework**.

B. Congress should establish and fully fund **an Environmental Biotechnology Regulatory Office (EBRO)** with a "special regulatory authority" to develop new risk assessment frameworks and grant regulatory approval for EMERs that fall outside of clear jurisdictional boundaries of the existing regulatory agencies.

C. Congress should authorize and fully fund the development of **EMER testing sites** for academic researchers and EMER developers to conduct field trials under contained conditions.

D. Regulatory agencies should create a **single, publicly accessible point of aggregation for EMER-related data**.

E. Funding bodies should increase **funding for basic research** on EMER impacts on natural environments.

F. Congress should increase **funding for communication efforts** between regulatory agencies, EMER developers, and the public.

Chapter 1: Introduction

From the birth of modern biotechnology half a century ago until the present day, the United States has developed a strong and thriving biotechnology industry that has allowed it to position itself as a world leader in this critical technology sector [1]. A major contributor to this historical success is the existence of a regulatory framework for biotechnology products that has resulted in decisions that have, to various degrees of success, ensured safety while allowing innovation to occur.

The United States government has recognized the need to update its regulatory framework over time in order to keep pace with the larger advancement of biotechnology. Since the 1986 publication of the Coordinated Framework for the Regulation of Biotechnology which outlined federal regulatory policy for biotechnology products, the framework has been updated in 1992 and in 2017 [2]. However, the rapid pace of scientific advances in fields such as gene sequencing, gene synthesis, and genome editing have led to a correspondingly rapid acceleration in biotechnology innovation over the past twenty years, which together place the field, today, in the early stages of a massive and transformative expansion [3]. This pace of progress is reflected in the fact that the past three presidential administrations have recognized the need for additional modernization of the Coordinated Framework, via the 2015 memorandum that led to the 2017 update and via Executive Orders 13874 in 2019 and 14081 in 2022 [2].

Within this context of biotechnology progress, **Engineered Microbes for Environmental Release (EMERs)** are an area exhibiting particularly rapid growth [4]. EMERs have the potential to have enormous global economic and societal impacts, by allowing biotechnology to be applied to new categories of application spaces such as infrastructure and clothing via engineered living materials, environmental detection of toxins or explosives via biosensors, microscale resource extraction via biomining, and attenuation of climate change via carbon sequestration or chemical fertilizer replacement [5].

The past three presidential administrations have recognized the need for additional modernization of the Coordinated Framework.

This wide diversity of application areas for EMERs places them at odds with a regulatory framework that was designed around more conventional biotechnology applications such as pesticides, drugs, agricultural chemicals, and food sources [3]. The multifaceted nature in which EMERs could interact with the public and natural environments raises challenging questions about whether and how they can properly fit into the existing regulatory framework. EMERs therefore raise the need for the development of new risk/safety assessment frameworks, or modifications of existing methods of review, to ensure effective regulation.

Direct application of the current biotechnology regulatory framework to emerging EMER products results in regulatory pipelines that are highly complex and can lead to high costs and long timelines in navigating the framework [4]. This stifles innovation in this sector, as the significant uncertainties and added costs to the product development pipeline are sometimes sufficient to end the commercialization of products with otherwise promising potential. Furthermore, complex and slow regulatory pipelines can erode public trust in the safety of approved products as well as the government's ability to regulate the products [6].

Successfully addressing these emerging regulatory challenges to promote innovation in EMER technology will create new opportunities for skilled jobs in research, manufacturing, and other biotechnology-related industries. In contrast, failure to act quickly and effectively in resolving the challenges of EMER regulation at this critical moment could have major consequences for both U.S. interests and global society as a whole.

These include:

1. EMERs are poised to be a major component of the biotechnology sector over the coming decades, and stifling innovation in this space could hamper U.S. national security interests via both a decrease in general economic competitiveness as well as the loss of scientific and technological talent to other countries that better support EMER innovation.

2. U.S. regulatory systems are often consulted by other geopolitical entities, and thus have the ability to help set global precedents for emerging technologies. This is particularly important for product classes like EMERs that will have a global reach, both due to the nature of their potential application areas (e.g., climate change mitigation, international shipping) as well as their intrinsic dispersibility as microscopic self-replicating organisms.

3. Many EMER products will address urgent issues related to mitigating the environmental impacts of climate change and other human activities such as mining, agriculture, and chemical manufacturing. U.S. failure to nurture responsible innovation in the EMER space could significantly delay this technology's ability to mitigate these impacts, thereby exacerbating their harms to both U.S. and global communities.

This report aims to accomplish two goals. First, it identifies the types of challenges that EMER products face in navigating the current federal biotechnology regulatory system (Chapter 5). Second, it presents actionable policy recommendations to the federal government, the biotechnology industry, and the wider scientific community about how to address these challenges (Chapter 7).

The remainder of the report is organized as follows:

- Chapter 2 defines the concept of an EMER and describes their properties and potential application areas.

- Chapter 3 provides some background on the U.S. federal biotechnology regulatory framework through the lens of EMER products.

- Chapter 4 examines some historical case studies of EMER product development and regulation.

- Chapter 5 describes specific ways in which the current U.S. regulatory framework will be challenged by the needs of rigorous EMER regulation, and summarizes current ongoing efforts by the federal government to address these challenges.

- Chapter 6 provides some concluding remarks.

- Chapter 7 presents the specific policy recommendations of this report.

Chapter 2: Background on EMERs

2.1: Definition of EMERs

We will begin by defining the terminology within Engineered Microbes for Environmental Release (EMERs). An EMER is, first and foremost, an engineered microbe (Figure 2.1a). Discussions surrounding engineered microbes typically use the term GEM (Genetically Engineered Microbe) or GMM (Genetically Modified Microbe), with the recognition that the terms "genetically engineered/modified" and "microbe" can themselves be ambiguous [7,8]. For our purposes, we will use the term "microbe" to refer to bacteria, archaea, and unicellular fungi, and we will consider a microbe to be engineered if it has undergone a process of intentional insertion, rearrangement, or deletion of genetic material via modern molecular biology techniques. There are many such techniques, and different choices of genetic engineering method can sometimes have consequences on the regulatory categorization of the resulting GEM.

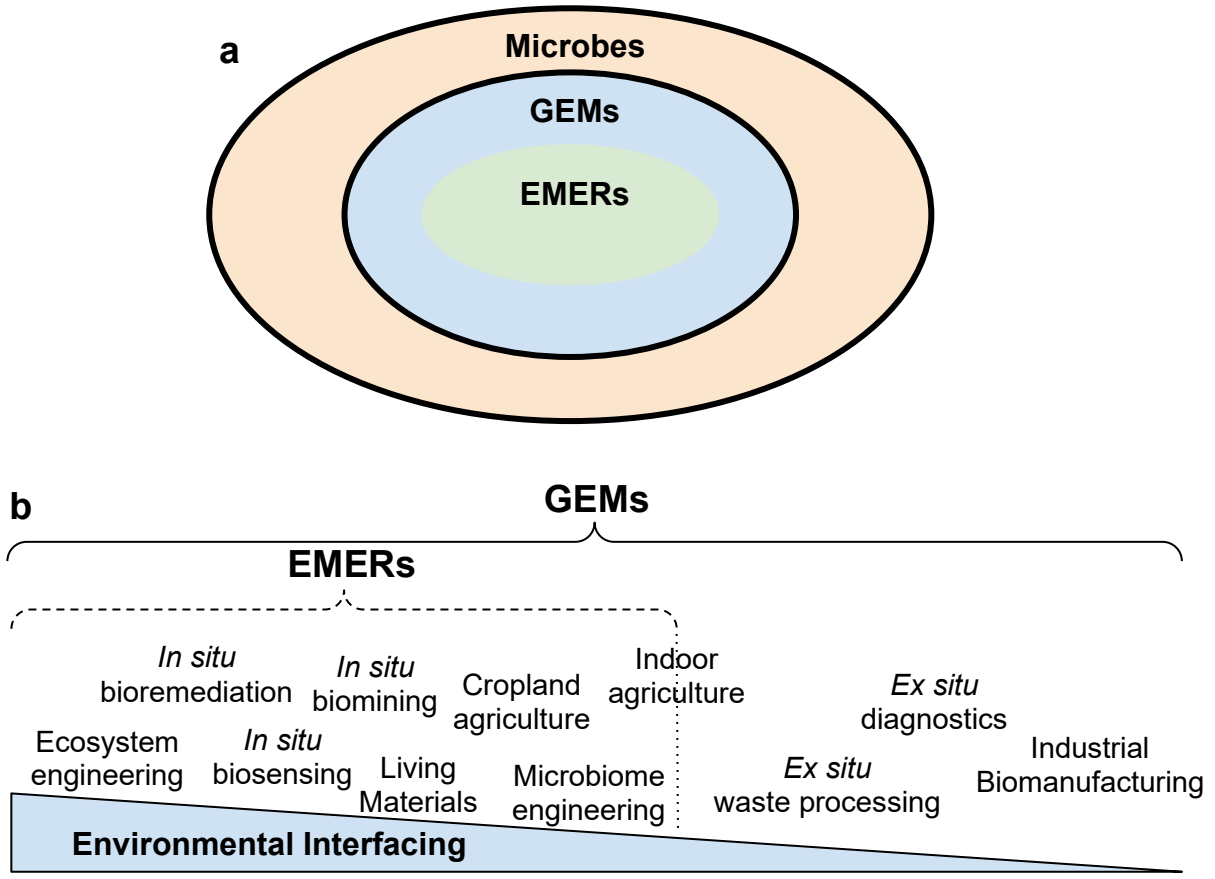

Figure 2.1: Defining Engineered Microbes for Environmental Release (EMERs). (a) EMERs are a subset of Genetically Engineered Microbes (GEMs), which are themselves a subset of microbes. Whether a particular GEM should be classified as an EMER is not always a sharp distinction. (b) The property of Environmental Interfacing, the extent to which the product will be exposed to the wider natural environment in its intended application, determines whether a GEM is an EMER or not. Different categories of applications exhibit different levels of Environmental Interfacing. GEMs developed for applications with high Environmental Interfacing are EMERs.

The notion of “for Environmental Release” is more nuanced, and is dependent on the application context for which the GEM was designed. We will invoke the concept of Environmental Interfacing [5], or the extent to which the microbe in its intended deployment environment is exposed to the wider natural environment, to describe when a GEM is considered an EMER (Figure 2.1b). It is important to note that there is no sharp boundary between EMERs and non-EMER GEMs, as “EMER” is a functional term that we use to highlight the specific product properties and regulatory considerations associated with the environmental release, specifically, of engineered microbes. As such, the specific risk assessment considerations unique to EMERs as opposed to non-EMER GEMs (i.e., those relating to the product’s impact on natural environments) will become less relevant as the Environmental Interfacing of a particular GEM’s intended application decreases.

Broadly speaking, a GEM intended to interact with a natural environment *in situ* will be categorized as an EMER. This includes application areas such as environmental remediation of contaminated environments, *in situ* resource extraction via biomining, detection of explosives or toxins via *in situ* biosensing, and any applications that involve applying the GEM to farmland, such as to fix nitrogen for crop growth to offset fertilizer use. GEMs used as the basis for engineered living materials, whether to serve directly as the structural basis for infrastructure (*e.g.,* self-healing concrete) or to supplement existing materials (*e.g.,* wearable biosensors on clothing or packaging, or corrosion-resisting biofilms on ships), would also typically be categorized as EMERs. GEMs used in gut microbiome engineering efforts, both for human health (*e.g.,* by secreting beneficial compounds in the gut) and for agricultural sustainability (*e.g.,* by reducing methane emissions from ruminants), should also be considered as EMERs because the GEMs will be able to enter the wider natural environment via waste streams.

In contrast, GEMs used in contained, closed application contexts are not EMERs. GEMs used in industrial biomanufacturing processes such as biofermentation are not EMERs because they are used only in closed bioreactors whose waste streams can be sterilized or otherwise treated to render the microbes incapable of replication. Similarly, diagnostic biosensors that operate by manual application of environmental samples to an otherwise-closed device are not EMERs because the GEMs themselves are not released into the wider environment. GEMs used in biomining efforts to process excavated ore on site, but in a contained facility rather than in the seam itself, would also not be categorized as EMERs.

Some application areas, however, defy clear categorization. Application of GEMs to indoor farming contexts such as hydroponic or greenhouse agriculture, for example, straddle the line between EMER and non-EMER categorization. If the produce is processed in such a way that the GEMs are removed from the produce before it leaves the contained area, then such a case would not be considered an EMER application. In practice, however, ensuring such containment would be difficult in such a context. Therefore, some risk assessment considerations relevant to EMERs should be applied when regulating such GEM usage.

Methods for genetically engineering microbes

The goal of genetically engineering microbes is to enable them to perform some function that is desired for the intended application, such as creating, sensing, or degrading a particular target compound. Endowing the microbe with this function is typically accomplished by either:

- Enhancing a microbe’s pre-existing ability to perform this function, for example by increasing its effectiveness or ensuring that it occurs only under a desired set of environmental conditions;
- Removing a microbe’s ability to perform one of its natural functions, if that function is undesirable for the end application;
- Providing the microbe with the ability to perform a wholly new function.

The genetic modifications themselves are conducted through a variety of methods which we can categorize into two broad classes. We will refer to these classes as targeted and untargeted approaches.

Targeted genetic modification approaches make use of enzymes which modify DNA in predictable ways to perform precise, designed modifications to a microbe's genome. Restriction enzymes, base editors, and CRISPR/Cas9 systems are examples of such DNA-modifying enzymes, originally found in nature, which have been repurposed for genetic modification in modern molecular biology. The modifications enabled by such systems include the ability to insert DNA sequences into targeted locations on the genome, remove targeted regions of the genome, and rearrange DNA sequences so that a target region is moved to a new genomic location.

The use of a taxonomic basis for this categorization presents many challenges, including the fact that the taxonomic designations themselves can change over time, altering whether a particular modification is classified as intergeneric or intrageneric.

In contrast, untargeted methods do not make use of specific, predesigned modifications to the microbe's genome. Instead, they rely on harnessing natural mutational processes to randomly generate the target function. Directed evolution, or laboratory evolution, is the main example of such methods. In these approaches, a large number of random mutations are generated, for example by the use of environmental stressors such as UV light or of mutation-inducing enzymes. This resulting "library" of mutants is then screened to assess which variants best perform the target function, and this variant is then used as the starting point for another round of mutation. By repeating these cycles of mutation and screening, one can eventually obtain a microbe that effectively performs the desired function. This procedure can be applied to specific genetic sequences in isolation, in which case the resulting gene would be inserted into a microbe via a targeted genetic approach, or on the microbe's genome as a whole.

From a regulatory standpoint, the Environmental Protection Agency (EPA) makes the distinction between organisms that have undergone **intergeneric** (sometimes referred to as **transgenic**) modifications and those that have undergone **intrageneric** (sometimes referred to as **cisgenic**) modifications. An **intergeneric** modification involves the stable introduction into an organism of genetic material derived from an organism from another genus or synthesized fully synthetically. In contrast, a modification is **intrageneric** if it only introduces genetic material from another species in the same genus or does not introduce any new genetic material at all (e.g., by deleting or rearranging the microbe's original genomic sequences).

GEMs created through intrageneric modifications are regulated differently than those created through intergeneric modification, under the reasoning that deletions and rearrangements of genomic material within a species, or between closely related species, are processes which occur more frequently in nature than between more divergent species [4].

In practice, however, the use of a taxonomic basis for this categorization presents many challenges, including the fact that the taxonomic designations themselves can change over time, altering whether a particular modification is classified as intergeneric or intrageneric [4].

2.2: Distinguishing properties of EMERs compared to alternative product classes

By virtue of being live microbes, EMER products differ in many ways from other classes of biological products, such as crops, and from nonbiological products. Below we describe some of the major differences, and the implications they have for risk assessments of EMERs.

The fundamental difference between living and nonliving products is the ability of living organisms to **self-propagate** via reproduction. As a consequence, a major regulatory consideration in the environmental deployment of living organisms is to assess the feasibility of containing the organism within the spatiotemporal confines of the intended application [6]. Assessing the extent of containment is particularly important for live microbial products, because of microbes' ability to reproduce asexually.

Another important distinction between microbial and nonmicrobial products is the **small size** of microbes. This makes them difficult to detect within environments without dedicated techniques such as DNA sequencing, which makes post-deployment monitoring of the product more challenging [5]. Furthermore, their microscopic size provides microbes with wide-ranging dispersal properties, by allowing them to be carried over long distances by wind and water [9]. When coupled with some microbes' ability to **sporulate** (to enter an inert state that can persist for long periods of time under strong environmental stressors), these properties allow microbes to potentially persist and spread across many types of environments.

Microbes, particularly bacteria, also frequently engage in **horizontal gene transfer**. This means that nonnative genetic sequences contained within an introduced microbe could be transferred to native microbes within that environment. Furthermore, genes from the native microbes could also be transferred into the introduced microbe. The many possible genetic interactions that can occur in this way compounds the uncertainties associated with releasing a nonnative microbe into an environment.

Microbes in nature often exist in multispecies communities called **consortia**. In some environments, these various species might be mutually dependent on each other for their survival, effectively making the consortium the fundamental unit of organization. In other environments, the species in the consortium might be able to exist independently. The fact that many future microbial products may be consortia, rather than individual species, will raise new types of considerations for proper risk assessment under a regulatory system designed around single-species products [3].

In application spaces where there may be few practical alternatives, the unique properties of microbes must be evaluated directly against the no-action alternative instead of against other types of solutions.

All of the properties described above apply to both EMERs and non-engineered microbes. While the act of genetically modifying a microbe to create an EMER will modify the types of activities that the microbe can perform, it generally does not confer additional categories of properties related to its environmental impact. As such, EMERs, as a class, do not intrinsically pose any additional categories of environmental or health hazards compared to non-engineered microbes. In fact, EMERs can be engineered to remove some of the general microbial properties that might be undesirable for environmental release. For example, replication-deficient strains of microbes can be engineered that remove their ability to self-propagate, and microbes can be engineered to resist or even prevent incoming and outgoing horizontal gene transfer [5].

Finally, we note that in some application areas, live microbial products are currently the only feasible approach to address the needs of the application. In application spaces such as *in situ* environmental bioremediation where there may be few practical alternatives, the unique properties of microbes must be evaluated directly against the no-action alternative instead of against other types of solutions [6].

Chapter 3: Background on the U.S. Biotechnology Regulatory System

3.1: EMERs and Risk Assessment Frameworks

The basic concepts of risk assessment

We begin this section by briefly summarizing the basic concepts of risk assessment, based on the 1983 National Research Council report on risk assessment [10]. Risk assessment in the United States is conducted through a process aimed at evaluating potential hazards and determining associated risks to human health, the environment, and other relevant factors. Safety assessment, on the other hand, involves risk mitigation considerations, such as the imposition of safety factors to account for uncertainties among individuals, populations, or species, and the imposition of containment procedures.

The first step in the process is hazard identification and characterization. Agencies identify and characterize potential hazards posed by substances, activities, or situations, using scientific literature and available data to determine whether specific chemicals, microorganisms, contaminants, or conditions are associated with adverse health effects or other risks.

Next, agencies assess the relationship between the magnitude of exposure to a hazard and an adverse outcome in a particular study—a step termed "dose-response assessment." This typically involves analyzing information from toxicological research, epidemiological studies, and other relevant information to quantify the impacts associated with different levels of exposure.

The actual risk assessment endpoints for an EMER deployment, i.e., the types of downstream impacts that could occur from the deployment, are not different from those for non-engineered microbial products.

Federal agencies then go about evaluating the extent and magnitude of potential human or environmental exposure to the hazard—be it a chemical or a microbe. This step, termed "exposure assessment" includes estimating exposure levels through various pathways, such as ingestion, inhalation, or skin contact, and assessing factors such as frequency, duration, and intensity of exposure.

Finally, agencies integrate the results of hazard characterization, dose-response assessment, and exposure assessment to characterize the nature and magnitude of risks. This "risk categorization" involves describing the potential health impacts and should include a full discussion of uncertainties and variability and how they could impact the likelihood of adverse outcomes.

Risk assessment considerations for EMERs

Potential hazards arising from the release of EMERs (and the environmental release of non-engineered microbes, more broadly) fall into two major categories: hazards to human or animal health and hazards to natural ecosystems. Hazards to human health have always been an important component of risk assessment for biotechnology products in general, regardless of whether they are intended for environmental release. As such, the direct human health risks associated with EMERs can be evaluated effectively under existing regulatory frameworks for biotechnology products.

The additional complexities in risk assessment of EMERs, as opposed to microbes used in contained environments, therefore center around their potential for impacting the natural ecosystems in which they would be introduced. It is important to emphasize that the actual risk assessment endpoints for an EMER deployment, i.e., the types of downstream impacts that could occur from the deployment, are not different from those for non-engineered microbial products [3]. In both cases, the salient hazard is that the introduced microbe could outcompete native microbes and essentially act as an invasive species–in North America alone, invasive plants and animals are estimated to have caused $120 billion in economic losses and pose primary extinction risks to about half of the threatened or endangered species in the United States [11].

Where EMERs differ from conventional microbes from a risk assessment standpoint is in exhibiting additional complexities and uncertainties in the risk of potentially reaching those endpoints [3]. The major challenge in performing reliable risk assessments of EMERs, therefore, lies in the difficulty of predicting the downstream ecological consequences of introducing a microbe into a particular environment. This highlights the need to advance our ability to make such predictions more reliably, for example by developing new measurement systems to estimate and bound estimates of the downstream consequences with empirical data.

Contextualizing the risks of EMER deployment

Many goals are infeasible to accomplish without the use of engineered microbes. Foregoing such interventions could potentially lead to much greater risks than from the microbial deployment itself.

The challenges associated with assessing and regulating EMER risk cannot, however, be considered in a vacuum. They need to be viewed in relation to risks that the world already lives with because of the frequent movement of microbes from their native habitats into new environments owing to natural causes and human activity.

To take soil microbes as an example: soil microbes can be naturally dispersed through wind, water, and animal activity [9]. Wind can carry spores and dust containing microbial organisms over long distances. Water can transport microbes downstream or through ocean currents. Animals, including insects, birds, and mammals, can carry soil and its microbial inhabitants on their bodies or in their digestive systems. Humans unintentionally move soil microbes through global trade, travel, and agriculture. Soil is also intentionally transported in large quantities for applications such as construction and environmental cleanup, which will also inadvertently transport its associated soil microbes as well. Movement of soil, plants, and livestock for farming can introduce soil microbes to new regions. What this means is that “non-native” microbes have been constantly moving into “new” environments for thousands of years.

While the existing acceptance of risk factors (existing large-scale movements of microbes) does not necessarily justify the adoption of additional risk factors (a targeted microbial deployment), it is nonetheless useful to factor this reality into consideration in regulating EMERs. In particular, because many of the potential risks of EMER deployment come from unpredicted ecological interactions, the fact that unintended microbial introductions are already happening frequently around the world can be leveraged as a starting point for developing more reliable predictions about the probability of such impacts.

Furthermore, any risks of deploying EMERs should also be weighed against the risks of not taking action. Many goals in application areas such as microbiome engineering are infeasible to accomplish without the use of engineered microbes. The cost of foregoing such interventions, for example when they target the impacts of the climate crisis, could potentially lead to much greater risks than from the microbial deployment itself.

3.2: EMERs and the Coordinated Framework

Biotechnology regulation in the United States

EMERs cannot rely on a long history of similar, successfully commercialized products to serve as precedent, as can be done for more conventional biotechnology products like genetically modified crop plants.

The regulatory framework for biotechnology in the United States was established in 1986 through the Coordinated Framework for the Regulation of Biotechnology. This framework designated three government agencies—the Environmental Protection Agency (EPA), the United States Department of Agriculture (USDA), and the Food and Drug Administration (FDA)—to oversee different aspects of biotechnology regulation based on product intent, claims, and potential unintended effects. Broadly speaking, EPA is responsible for environmental safety, USDA regulates agricultural aspects, and FDA ensures safety and efficacy of biotechnology products in food, animal feed, and medicine [2].

A defining feature of the Coordinated Framework is that it was designed with the understanding that pre-existing statutes were sufficient to meet the regulatory needs of biotechnology products, and that the pre-existing agencies would jointly regulate biotechnology products according to their conventional purviews [12]. Because each regulatory agency is governed by different statutes that apply different risk assessment standards requiring different types of data, the Coordinated Framework can become very complex for a new product entering the regulatory process (Figure 3.1).

This challenge is particularly true for EMERs, as they cannot rely on a long history of similar, successfully commercialized products to serve as precedent, as can be done for more conventional biotechnology products like genetically modified crop plants. As such, it can be difficult to predict which administrative unit of the federal government would have the statutory authority to claim a particular EMER product, or by which assessment methodology the product would be evaluated.

In the following section, we briefly describe some of the statutory and regulatory processes associated with the major federal regulatory agencies (e.g., EPA, USDA, and FDA) that address natural or genetically engineered microbes (GEMs) and therefore may be relevant to the regulation of a particular EMER (for a larger list of potentially relevant statutes, see Table 3.1). However, developers of EMERs with particular intended uses should contact regulators directly for advice.

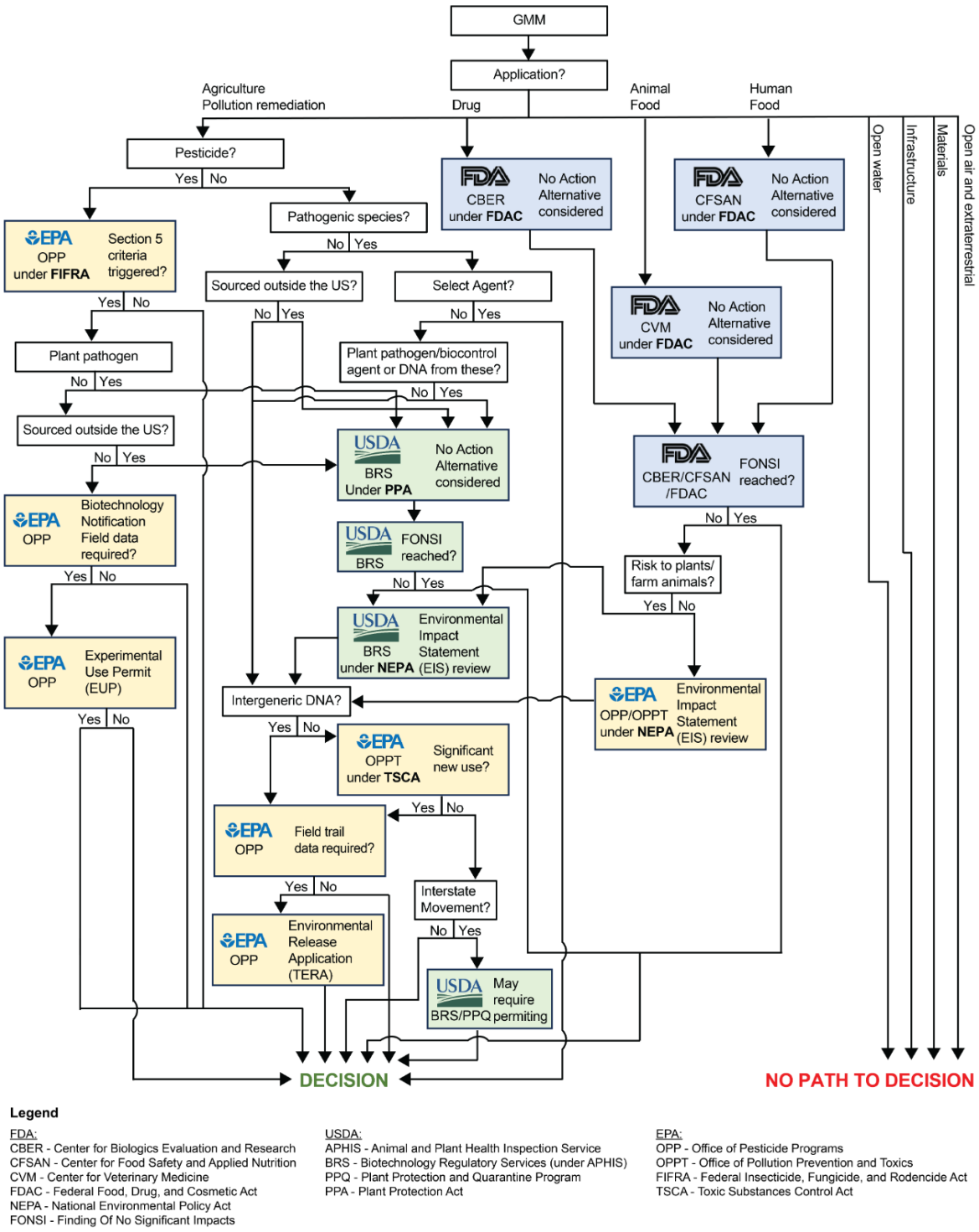

Fig 3.1: The various regulatory triggers that define the paths that a genetically modified microbe (GMM) developed as a product intended for commercialization might take through the Coordinated Framework. “No Path to Decision” indicates the lack of a clear regulatory precedent for such a microbial product. Figure reproduced with permission from Chemla, Y., Connor J. Sweeney, Christopher A. Wozniak, and Christopher A. Voigt. Engineering Bacteria for Environmental Release: Regulatory Challenges and Design Strategies. Nature Microbiology, **in Revisions** (2024). [PREPRINT: Yonatan Chemla, Connor J. Sweeney, Christopher A. Wozniak, and Christopher A. Voigt, Engineering Bacteria for Environmental Release: Regulatory Challenges and Design Strategies. *Authorea.* June 25, 2024. DOI: 10.22541/au.171933709.97462270/v1]

TABLE 3-1 Statutes and Protection Goals Related to the U.S. Environmental Protection Agency (EPA), the U.S. Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA) for the Regulation of Biotechnology Products

Agency	Statute	Protection Goal
EPA	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)	Prevent and eliminate unreasonable adverse effects on the environment • For environmental and occupational risks, this involves comparing economic, social, and environmental risks to human health and the environment and benefits associated with the pesticide use. • For dietary or residential human health effects, the sole standard is the "safety" of all the combined exposures to the pesticide and related compounds.
EPA	Federal Food, Drug, and Cosmetic Act (FDCA)	Ensure that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.
EPA	Toxic Substances Control Act (TSCA)	Prevent the manufacture, processing, distribution in commerce, use, or disposal of chemical substances, or any combination of such activities with such substances, from presenting an unreasonable risk of injury to health or the environment, including an unreasonable risk to a potentially exposed or susceptible population, without consideration of costs or other nonrisk factors.
FDA	FDCA	Ensure human and animal food is safe, sanitary, and properly labeled. Ensure human and animal drugs are safe and effective. Ensure the reasonable assurance of the safety and effectiveness of devices intended for human use. Ensure cosmetics are safe and properly labeled.
FDA	Public Health Service Act	Ensure the safety, purity, and potency of biological products.
USDA	Animal Health Protection Act (AHPA)	Protect livestock from animal pest and disease risks.
USDA	Plant Protection Act (PPA)	Protect agricultural plants and agriculturally important natural resources from damage caused by organisms that pose plant pest or noxious weed risks.
USDA	Federal Meat Inspection Act	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Poultry Products Inspection Act	Ensure that the United States' commercial supply of meat, poultry, and egg products is safe, wholesome, and correctly labeled.
USDA	Egg Products Inspection Act	
USDA	Virus-Serum-Toxin Act	Ensure that veterinary biologics are pure, safe, potent, and effective.

SOURCE: EOP (2017:9).

Table 3.1: Statutes relevant to biotechnology regulation under the Coordinated Framework. Reproduced with permission from the 2017 National Academies report on "Preparing for Future Products of Biotechnology" [3].

USDA regulations pertinent to EMERs

The United States Department of Agriculture (USDA) primarily regulates GEMs under the authority of the Animal and Plant Health Inspection Service (APHIS). APHIS derives its authority to regulate biotechnology products from the Plant Protection Act. As such, USDA regulations for GEMs place a large focus on risks to plant health, alongside broader risks to agriculture and the environment.

Permitting and Notification Requirements: Developers of GEMs that may impact plant health or agriculture must submit permit applications or notifications to APHIS. Permit applications are required for field trials or experimental releases of GEMs that may have environmental implications or interactions with plants. Notifications are required for certain low-risk activities involving GEMs, such as contained laboratory research.

Risk Assessment and Environmental Impact Analysis: APHIS conducts risk assessments and environmental impact analyses to evaluate potential risks associated with GEMs. Risk assessments consider factors such as the genetic characteristics of the microbe, potential for horizontal gene transfer, effects on non-target organisms, and potential impacts on agriculture and ecosystems.

Containment and Biosecurity Measures: APHIS may impose containment and biosecurity measures to prevent the escape or unintended spread of GEMs into the environment. Containment protocols and operational controls are implemented to minimize potential risks associated with the use and release of GEMs.

FDA regulations pertinent to EMERs

Potential EMER products that would fall under FDA authority would most likely be classified as a drug (any substance that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease) or a food additive (any substance that is reasonably expected to become a component of food).

Live Biotherapeutic Products (LBPs): The FDA Center for Biologics Evaluation and Research defines an LBP as a non-vaccine biological product that contains live organisms and “is applicable to the prevention, treatment, or cure of a disease or condition of human beings.” LBPs that meet the FDA definition of a drug cannot be used in interstate commerce without explicit FDA approval or the existence of an Investigational New Drug (IND) application. FDA typically assesses genetically engineered LBPs under the same guidelines as non-engineered LBPs, based on the reasoning that genetic engineering itself does not intrinsically increase safety concerns associated with the product [13]. However, additional characterization data pertinent to the genetic modifications themselves may need to be submitted.

New Animal Drug Approval (NADA): If a microbe is intended for use in animal feed or as a veterinary drug, developers must seek approval from the FDA's Center for Veterinary Medicine (CVM). This typically involves submitting a new animal drug application (NADA) or an abbreviated new animal drug application (ANADA), depending on the specific circumstances.

Food Additive Petition (FAP): If a microbe is intended to be used as a food additive, the developer may need to submit a food additive petition to the FDA. This petition must include scientific data demonstrating the safety and efficacy of the microbe for its intended use in food production. The FDA evaluates the petition and may approve the use of the microbe as a food additive if safety criteria are met.

Generally Recognized as Safe (GRAS): If a microbe intended to be used as a food additive is designated as GRAS (i.e., it is “generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use”), then the product is exempt from the need to submit a FAP. Developers can submit a GRAS Notice to FDA to inform the agency that a food additive is GRAS, upon which FDA will assess the notice to determine if it has provided sufficient information to support its conclusion. FDA

maintains a list of all GRAS Notices since 1998, as well as the agency's response letters, in the GRAS Notice Inventory [14].

EPA regulations pertinent to EMERs

The Environmental Protection Agency (EPA) regulates GEMs under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), focusing on assessing and managing potential risks to human health and the environment associated with their manufacture, use, and disposal, and under the Toxic Substances Control Act (TSCA).

Under FIFRA:

Microbial pest control agents (MPCAs), microbes intended for use as pesticides, are regulated under FIFRA by EPA. The data requirements for EPA risk assessments of genetically engineered MPCAs are the same as those for non-engineered MPCAs, although additional data requirements may be imposed on a case-by-case basis [12].

Field Trial Approval: Unless subject to explicit exemptions, any experimental field tests of genetically engineered MPCAs require prior notice and approval by EPA via the Biotechnology Notification Process (BNP). Large field trials (over 10 acres of land or 1 acre of aquatic environment) may additionally require an Experimental Use Permit (EUP). The data requirements for BNPs and EUPs include information about the product's persistence within the environment and potential adverse impacts to human and environmental health.

Pesticide Registration: After an MPCA moves beyond the experimental testing stage, a developer can apply to register it as a pesticide under FIFRA. The data requirements for pesticide registration are similar in nature to those of BNPs and EUPs, but with more rigorous standards and a greater emphasis on the potential for long-term off-target effects. All pesticide registrations under FIFRA are subject to periodic review and re-registration.

Risk Assessment and Management: Unlike those of most U.S. environmental statutes, FIFRA assessments of MPCAs evaluate both their risks and benefits to human health, the environment, and socioeconomic factors, rather than being exclusively precautionary assessments that only evaluate risk [12].

Under TSCA:

TSCA is used as a gap-filling statute that covers biotechnology products that are not regulated by other statutes. However, although GEMs with intergeneric modifications are subject to TSCA review, non-intergeneric GEMs and naturally-occurring microbes are exempt [12].

Microbial Commercial Activity Notice (MCAN): Companies planning to manufacture or import new GEMs must submit a microbial commercial activity notice (MCAN) to the EPA. The MCAN includes information on the microorganism's identity, intended uses, production volumes, potential exposure scenarios, and any available toxicity data. The EPA evaluates the MCAN to assess potential risks to human health and the environment associated with the new microorganism.

MCAN Exemptions for Research Purposes: Research activities for GEMs that are conducted within contained structures and subject to regulation by another Federal agency are exempt from the MCAN reporting requirement. Research activities for GEMs in open environments, such as field trials, can also be exempt from MCAN reporting requirements but must instead submit a TSCA Experimental Release Application (TERA). EPA must approve the TERA before the experiment can proceed. However, as of 2012, there are two bacterial strains for which EPA has determined that TERAs do not to be submitted for field trials:

Bradyrhizobium japonicum and *Rhizobium meliloti* [12]. This TERA exemption only applies for field trials that satisfy additional constraints, such as a maximum test size of 10 acres and the use of sufficient containment measures for the microbes.

Risk Assessment: As with FIFRA, TSCA is a risk-benefit statute that weighs a product's risks to human and ecosystem health against the socioeconomic benefits of its use. TSCA assessments permit the manufacture of the GEM if EPA determines that the GEM "presents no unreasonable risk of injury to human health or the environment". If EPA determines that such a risk exists, or if there is insufficient information in the application to determine this, then it will prohibit or restrict the manufacture and usage of the GEM accordingly.

General federal regulations pertinent to EMERs

All potential EMER products must also comply with broader federal statutes like the **National Environmental Policy Act (NEPA)** and the **Endangered Species Act (ESA)**. If a regulatory agency determines that an EMER under review may be impacted by one or more of these acts, additional federal agencies with the relevant expertise (such as the Fish and Wildlife Service or the National Marine Fisheries Service) would be consulted and incorporated into the regulatory process. Finally, in addition to federal regulations, EMERs may also need to undergo additional reviews for compliance in certain states that have their own environmental and health safety statutes.

Chapter 4: Historical Case Studies of EMER Product Development

In this chapter, we will discuss some concrete examples of EMER products that were developed, entered the regulatory pipeline, and were or were not commercialized. In doing so, we will illustrate the various types of factors that can potentially prevent an EMER product from successful usage in a target application area.

Frostban: An EMER to protect crops from frost damage

Frostban was one of the first EMER products to go through the regulatory review process, and as such had to contend with a combination of highly cautious regulation in the absence of precedent and much public concern due to its visibility.

The case of Frostban was the first instance in the history of EMERs that showcased the multifaceted interactions between developers, regulatory agencies, and public groups that lead to complex challenges with properly regulating their use. In this section we briefly summarize this history, as related by Skirvin et al. [15].

In the 1980s, a company called Advanced Genetic Sciences (AGS) developed a genetically engineered microbe with the aim of protecting crops from frost damage. The specific bacterium used was *Pseudomonas syringae*, which lives on the leaves of many types of crop plants. *Pseudomonas syringae* naturally produces a protein on its exterior which promotes frost formation via ice nucleation. AGS genetically modified *Pseudomonas syringae* to create a strain that produces reduced levels of ice-nucleating proteins. By spraying this “ice-minus” strain onto crops, the ice-minus strain could potentially outcompete the natural, frost-promoting strain on the crop leaves and thereby protect the crop from frost damage.

Frostban was one of the first EMER products to go through the regulatory review process, and as such had to contend with a combination of highly cautious regulation in the absence of precedent and much public concern due to its visibility. Critics were worried that the modified bacterium could affect non-target organisms and ecosystems such as honeybees. Furthermore, because ice nucleation is a critical part of the cloud formation process, members of the public expressed concerns about the EMER’s impact on rainfall patterns if it were released into the atmosphere. The actions of AGS itself during this period, for example by stretching the limits of permitted testing guidelines for field trials and in devoting insufficient efforts to public communication and education, also contributed to the challenging and controversial review process.

The controversy surrounding Frostban prompted considerable scrutiny by regulatory agencies. The U.S. Environmental Protection Agency (EPA) ultimately approved limited field trials of Frostban in California and a few other states but imposed strict regulations and monitoring requirements. Despite initial promise, Frostban did not prove to be commercially viable due to issues with effectiveness, public opposition, and regulatory challenges that led the company to discontinue its efforts to commercialize Frostban by the mid-1990s.

EMERs for Bioremediation

The history of EMERs is closely tied to the history of bioremediation (the use of biological organisms to reduce the concentration or toxicity of an environmental pollutant), and the field illustrates many of the hurdles that have traditionally held back EMERs from commercialization [6]. In this section we briefly summarize some examples in this history.

One of the first genetically engineered microbes, created by Ananda Chakrabarty in 1971, was developed to break down crude oil. As was the case with Frostban, however, a combination of overly cautious regulatory requirements and public concerns about the novel technology prevented the microbe from being commercialized. Despite the fact that the engineered strain was 10 to 100 times more effective at degrading oil than its natural counterparts, the strain was never deployed in a bioremediation setting [16].

As a result of this demanding process, many researchers opt to focus on utilizing naturally occurring microbes for commercial production instead of engineered microbes, essentially abandoning the promise of innovative new biotechnologies due to regulatory realities.

Although biotechnology companies placed much effort into developing EMERs for bioremediation during the 1980s and 1990s, these EMERs were similarly impeded by strict regulatory requirements and not commercialized. The example of an EMER developed to degrade Agent Orange, a toxic defoliant that the United States used during the Vietnam War, provides an illustrative example. EPA regulators at that time required an assurance that the toxin-degrading genes could not be transferred into pathogenic bacteria in the environment, and that these pathogenic bacteria would not be able to utilize these genes to make use of Agent Orange as a food source. Demonstrating the unlikelihood of such an impact was infeasible for the developers, and so the product was never deployed [16]. However, it is unclear the extent to which the larger assessment weighing the potential risks of the EMER's usage against the existing risks of the Agent Orange's persistence within the environment was factored into this process.

In the rare cases when EMERs have been deployed for bioremediation purposes, they have been shown to be effective in removing the toxin from the treated environment. For example, in 1989, Estonia experienced a major environmental disaster in the aftermath of a fire that burned in the world's largest oil shale mine for 81 days, causing extensive water pollution from the release of contaminants like phenol. Scientists engineered the bacterium *Pseudmonas putida* to degrade phenol and released it into the mine site, where it significantly reduced phenol levels [4]. Six years after this release, however, the genetic pathway for phenol degradation that was introduced into the EMER was detected in other bacteria within the Purtse River watershed, indicating that horizontal gene transfer had occurred between the EMER and the native soil microbes, conferring the native microbes with the ability to degrade phenol [17]. Whether this gene transfer event led to any tangible ecological harm to the native microbial community, however, is not yet known.

These examples illustrate that although EMERs can be effectively used for bioremediation, research is necessary to understand their possible intended and unintended effects across various environments before they can be widely deployed. However, the current regulatory framework often presents challenges in obtaining government permits for the necessary experiments, resulting in a time-consuming and complex process [6]. The Toxic Substances Control Act (TSCA) requires submission of multiple documents to initiate a detailed review of potential health and environmental impacts before pilot experiments with EMERs are allowed. As a result of this demanding process, many researchers opt to focus on utilizing naturally occurring microbes for commercial production instead of engineered microbes, essentially abandoning the promise of innovative new biotechnologies due to regulatory realities.

Box 4.1: Biological Nitrogen Fixation

Christopher A. Voigt and Yonatan Chemla, Massachusetts Institute of Technology

Nitrogenous fertilizers are essential for achieving high crop yields. However, ammonia synthesis by the Haber Bosch process has high environmental costs: it consumes 2% of global energy, produces 5% of greenhouse gas emissions, and is a major water pollutant. Biological nitrogen (N) fixation, performed by microbes, eliminates these issues. N-fixing microbes have been used to inoculate legumes for over 100 years [18] and they are available to consumers in most farming stores. However, naturally N-fixing microbes repress N fixation in the presence of the ammonia found in synthetic N fertilizers and do not fix N at all for cereals. Since the 1976 Asilomar conference, it has been recognized that engineering microbes to enable N fixation for cereals would have a major global impact.

In the 1980-1990s, several EMERs were developed to improve N fixation and remove ammonia repression (Figure 4.1). The first fields trials were conducted in 1988 by BioTechnica Inc. with a *Rhizobium meliloti* strain engineered to contain an extra copy of its native *dctABD* genes to improve its ability to grow on cereal roots [19-21]. This strain showed higher efficacy in the greenhouse, but the field trial results were not published. A variant of this strain was then constructed with intergeneric modifications that used the *dct* genes from another *Rhizobium* species and added the *aadA* antibiotic resistance gene to monitor the strain's field survival and performance [20-22]. In 1989, 1990, and 1992, field trials of this EMER with alfalfa showed increased colonization and yields after 30 days.

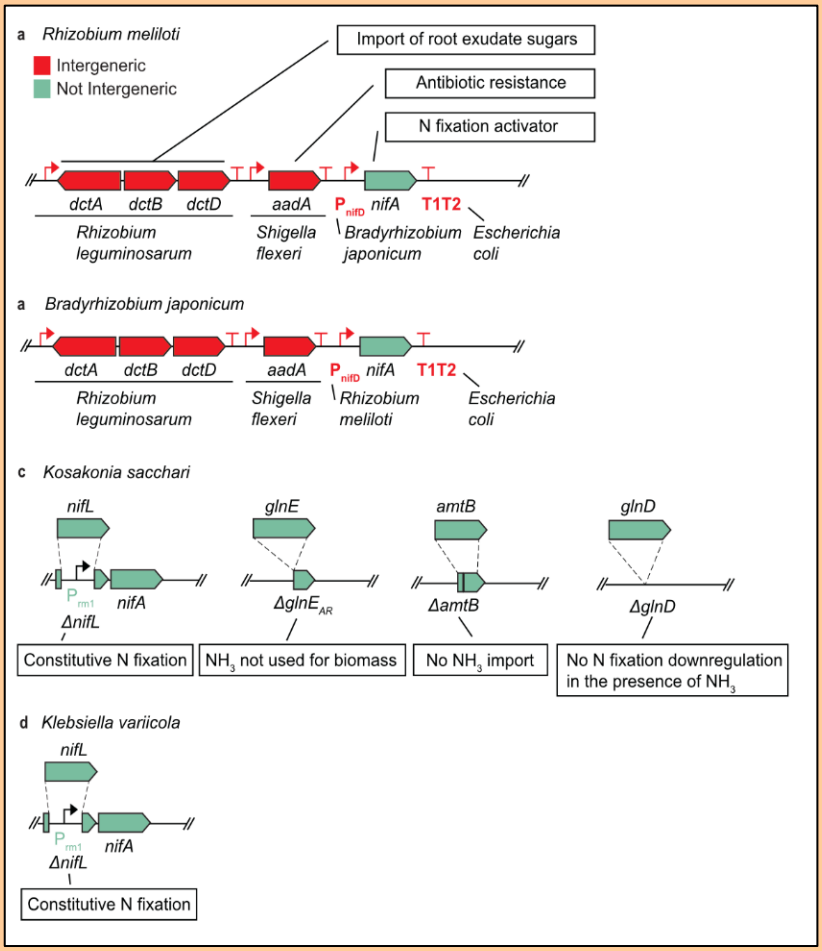

Figure 4.1: Field-tested N fixation genetic designs. Constructs are arranged by the order of their release. **a.** *R. meliloti* in 1992 on alfalfa fields. ***b.*** *B. japonicum* in 1989, 1990, & 1993 in soybean fields. **c.** *Kosakonia sacchari* and **d.** *Klebsiella variicola* in 2018 & 2019 in maize fields.

The bacterium *Bradyrhizobium japonicum* was then engineered to contain these genetic changes, and to additionally alter the regulation of the *nifA* gene (which activates N fixation) so that it is expressed constitutively, even in the presence of synthetic N fertilizer [23]. Field trials took place in 1989, 1990, and 1993 in soybean fields [21,22]. Between 1993 and 1996, trials were conducted on five U.S. sites to assess the EMER's effectiveness in colonizing alfalfa roots and increasing yields [21,23]. In 1994, another field trial tested five different *Bradyrhizobium japonicum* strains, modified only with the *aadA* gene without N fixation-associated genes, to assess their survival and monitorability in soybean fields. These trials ultimately led to regulatory approval for producing up to 500,000 pounds of the product annually. While the data from these field trials were never made public, these EMERs were not commercialized as the company did not feel the product was sufficiently efficacious.

Several decades later, a strain of *Klebsiella variicola* was isolated from corn roots and a strong constitutive promoter was moved in front of the *nifA* gene from another location in the strain's genome, which both increased *nifA* expression and inactivated *nifL*, which represses N fixation [24]. In 2018 and 2019, field tests with corn were performed with this "remodeled" bacterium, which showed elevated levels of N fixation and increased crop yields [24]. Later, a similar modification was done in *Kosakonia sacchari* in addition to several gene deletions designed to reduce the import and assimilation of ammonia [25]. Field trials with this EMER showed increased maize yields with reduced in-field variability. Due to the nature and function of the edits, these strains were determined not to be subject to regulation by USDA Biotechnology Regulatory Services as a genetically modified organism. The EPA confirmed that these microbes are not subject to regulation under FIFRA as they fall within an excluded category: "a plant inoculant product consisting of microorganisms to be applied to the plant or soil for the purpose of enhancing the availability or uptake of plant nutrients through the root system." In addition, the microbes are not subject to EPA/TSCA as they do not contain intergeneric modifications. These EMERs were registered at the state level by Pivot Bio, commercialized in 2019, and are now in wide use in the United States. Together, they are part of the ProveN40 product, which reduces the need for nitrogenous fertilizer by up to 20%.

Many additional improvements to N fixing EMERs are currently infeasible to implement without intergeneric modifications. For example, the nitrogen fixation genes from microbes with the highest N fixation activity could be moved into microbes which most reliably coat cereal roots to enable the "best of both worlds" [26-28]. Building on the strategy of the *dctABD* genes, additional metabolic pathways could be introduced into the microbes to enable them to make full use of the compounds secreted by plant roots [29]. Additional traits, such as the production of antifungals, could be "stacked" with N fixing EMERs to make them more effective bio-inoculants [30]. Safety switches could be added so that the EMER stops growing after a defined period or once an agrochemical is removed [31-34]. The EMERs could also be engineered to create synthetic symbiotic interactions with a plant, which would lock them to an engineered crop so that when the plants are removed the EMERs are as well [35]. Finally, the tracking of EMERs in the field could be improved using DNA barcodes. Simplifying the regulatory assessment process for EMERs with intergeneric modifications would therefore enable the development of more-effective and lower-risk products that translate directly into energy savings and environmental benefits.

Box 4.2: A Potential Future EMER Product Based on Horizontal Gene Transfer

Bruce A. Hay, California Institute of Technology

Here, we present a speculative but plausible scenario describing an EMER product whose mode of operation relies on horizontal gene transfer of an engineered genetic module into a native soil microbiome. The goal of this exercise is to raise questions about how such a product would and should be regulated under current or future regulatory frameworks and to illustrate an example of the diversity of biotechnology product modalities that EMERs can enable.

The goal of our hypothetical product is to carry out bioremediation of hydrocarbons found in soil as a byproduct of fossil fuel extraction. Targets of interest include decommissioned oil wells located near or within urban environments. The product itself involves a multi-gene cassette located on a conjugative plasmid. It includes genes isolated from multiple non-indigenous organisms and is therefore transgenic. Several of these genes have also undergone directed evolution and thus are novel. Expression of the cassette in bacteria results in degradation of multiple hydrocarbons, products of which can be used as an energy source by the bacteria.

Laboratory experiments using soils from target environments suggest that hydrocarbon removal is only significant when the plasmid is transferred to the indigenous soil microbes. Because these microbes are unculturable, *in situ* horizontal gene transfer is the only practical way to generate these hydrocarbon-degrading strains. Existing knowledge about the enzymatic pathways suggest that the plasmid is unlikely to spread to high frequency in the soil microbiome in the absence of hydrocarbons. Consistent with this hypothesis, the initial laboratory experiments showed that the frequency of the plasmid decreased as the level of hydrocarbons dropped to undetectable levels over 4 weeks, although the plasmid itself was still detectable via PCR 12 weeks after the initial inoculation. Preliminary safety tests inoculating the plasmid-carrying donor strain into mice showed that transfer of the plasmid occurs to some resident gut microbes, but no ill health effects were observed, and the plasmid ultimately becomes undetectable.

Typical strategies for biocontainment in large open field environments are either impractical (e.g., engineered auxotrophy) or will inevitably fail in large populations (e.g., transgene-based kill switches). Instead, the product includes a 2nd generation conjugative plasmid that can be released into the environment after bioremediation is complete. This plasmid lacks the hydrocarbon-metabolizing cassette and instead contains a targeted DNA nuclease whose only function is to promote the loss of the original plasmid when both plasmids are present within the same cell. Laboratory experiments suggest that this system can completely reduce the original plasmid to undetectable levels within 10 weeks, but it does not return the soil microbiome to a pre-transgenic state as the 2nd generation plasmid itself persists in many of the microbes.

We now ask: How should this product be regulated and deployed? What sort of additional testing, if any, ought to be conducted as part of the risk assessment process? How does the way in which this hypothetical product would pass through the current regulatory system, or proposed future regulatory systems, differ from the answers to the above?

Chapter 5: Emerging Challenges for the EMER Sector

5.1: Regulatory challenges

Many of the fundamental challenges with regulating EMERs under the Coordinated Framework can be traced back to two decisions that were made during its initial inception in 1986 [36]. First, that existing statutes for the regulation of non-biotechnological products (such as pesticides) were sufficient to regulate biotechnology products. Second, that the existing federal regulatory agencies should jointly regulate biotechnology products according to their respective regulatory purviews.

While these choices may have been justified in 1986, today's biotechnology landscape brings entirely new classes of products which do not neatly fall into pre-existing regulatory categories [3]. EMERs embody many of these new product classes. Consider, for example, an engineered microbe intended to act as a drug by residing within the human gut and producing a beneficial compound. This microbe has a path, via waste streams, to enter into natural environments, self-propagate there, and become resident in those ecosystems, which brings a set of regulatory considerations that are not shared by conventional drugs under FDA purview. Or consider the example of engineered microbes embedded into clothing to endow it with deodorizing properties. Transgenic organisms that cross state lines fall under EPA jurisdiction by default, but what if these microbes were engineered using only cisgenic modifications? For such unconventional product classes, it can be unclear which regulatory agencies have, or ought to have, regulatory jurisdiction over the products.

Statutory changes to the Coordinated Framework and biotechnology regulation will be needed to address these issues.

The major challenges associated with EMER regulation under the Coordinated Framework arise from two key consequences of the Coordinated Framework's organization. First, the existence of **jurisdictional overlaps** between the agencies creates uncertainties about where candidate products fall within the regulatory framework [36]. This is particularly true for EMER products, which will always have a broader environmental impact consideration that will have relevance to the domain of EPA in addition to their intended application context. Jurisdictional overlap also creates divergence points by which two very similar products might undergo very different regulatory paths depending on whether the jurisdictional overlap was resolved in the direction of one agency or another [37]. The fact that each agency undergoes regulatory assessment in different ways, governed by different statutory requirements, further accentuates the consequences of such divergence points. The result is that the regulatory process for EMER developers is filled with uncertainties and can require the product to simultaneously satisfy varying regulatory requirements for risk assessments across multiple different agencies [36]. This adds a large amount of time and cost to the regulatory process which can be particularly burdensome to small developers.

Second, the reliance on existing regulatory statutes to govern biotechnology products creates scenarios with **misaligned regulatory triggers** for biotechnology products [36]. Regulatory triggers are descriptions of which regulatory statutes apply to a particular product, based on its properties or its intended uses. As technological progress enables the creation of new types of products to address new types of application areas, regulatory triggers for statutes written prior to these developments may no longer appropriately capture the full space of product classes.

EMERs are particularly susceptible to this challenge because they can frequently fall into novel and unconventional product application classes, such as engineered living materials. Such products would likely fall under the jurisdiction of EPA under TSCA, which has taken the role of a "catch-all" statute [12]. As more types of product classes emerge, the appropriateness of applying a statute written to control toxic substance usage to broad and diverse classes of products will become increasingly challenged.

Because these regulatory triggers arise from the regulatory statutes themselves, statutory changes to the Coordinated Framework and biotechnology regulation will be needed to address these issues described above, as well as additional limitations of the current regulatory framework (Box 5.1).

5.2: Scientific challenges

Another major challenge facing EMER developers is the fact that the rigor of the risk assessment frameworks applied to a particular EMER product is sometimes misaligned with scientific consensus on the level of risk posed by the product.

Distinctions such as those between intergeneric versus intrageneric modifications, though based on sound reasoning about the likelihood of such modifications occurring naturally, bear little or no intrinsic bearing on the potential for an EMER to cause ecosystem harm.

A major example of such a misalignment comes from process-based triggers for engineered microbes based on the nature of how they were genetically engineered. Distinctions such as those between intergeneric versus intrageneric modifications, though based on sound reasoning about the likelihood of such modifications occurring naturally, bear little or no intrinsic bearing on the potential for an EMER to cause ecosystem harm [4]. Despite this fact, these classifications correspond to regulatory triggers that can give functionally equivalent products vastly different types of risk assessment procedures [37]. An inevitable consequence of such a regulatory structure is that some products will be assessed to a more lenient standard than would be desired, and that other products will be assessed to a more rigorous standard than necessary, placing an undue burden on the regulatory agencies and stifling developer-based innovation in this space.

Despite the existence of scientific consensus on points such as the intergeneric-intrageneric distinction, there are still many properties of EMER usage that do not have an adequate scientific knowledge base to form a consensus [4]. General principles about the persistence and dispersal of nonnative microbes introduced into environments, or the persistence and dispersal of engineered DNA from EMERs in those environments, are still greatly understudied [5]. As a consequence, each EMER product entering the regulatory framework must "reinvent the wheel" in characterizing its, for example, dispersal and persistence properties, inflating the burden of proof for developers during the risk assessment process. The existence of a more mature knowledge base about these properties could lessen this burden for individual EMER assessments and also serve as the basis for a rethinking of wider risk assessment frameworks for EMERs.

Unfortunately, there are many factors that make it difficult to develop such a scientific knowledge base. One is that the use of EMERs for basic scientific research can be challenging, as academic field trials must still obtain regulatory approval through similar channels to those for products intended for commercialization [12]. The fact that a research program proposing to release microbes with a benign genetic modification such as the expression of a fluorescent reporter protein must obtain approval under the rigorous requirements of TSCA, for example, makes it highly impractical to conduct basic research aimed at developing these very questions that would benefit EMER regulation [4].

Box 5.1: Governance Limitations of the Coordinated Framework's Regulation of EMERs

Alejandro E. Camacho, University of California, Irvine

Under the Coordinated Framework—the core system for regulating biotechnology in the U.S. for almost four decades—EMERs may be regulated by the EPA, FDA, and/or USDA, but only to the extent that pre-existing statutory authority allows such regulation. EPA may regulate an EMER characterized as a federal pesticide; FDA may regulate an EMER characterized under federal law as a food or drug pesticide; and USDA may regulate an EMER if it is a biopharmaceutical or poses a risk to agricultural plant and livestock products. As such, the Coordinated Framework was only ever intended as an inter-agency structure for organizing certain activities of three federal agencies. And the Coordinated Framework's initial focus, as well as that of later modifications, has largely been on managing jurisdictional overlap between the EPA, FDA, and USDA that may cause permitting inefficiencies, either by reducing such overlap or coordinating oversight.

However, this limited patchwork does not address other core problems of U.S. biotechnology policy. First, gaps in authority between EPA, FDA, and USDA remain that might allow some EMER technologies to evade review. Second, the EPA, FDA, and USDA lack expertise over important ecological and biodiversity risks and benefits raised by EMERs. There are many regulators with at least some such expertise, including Fish and Wildlife Service, National Marine Fisheries Service, U.S. Geological Survey, federal land management agencies, and many Tribal and state authorities. Many of these also are likely to have oversight responsibilities over EMER deployment. Instituting a range of coordination mechanisms that integrate these other authorities into the Coordinated Framework will better advance its goals of streamlining and risk reduction.

Third, the Coordinated Framework's focus is exclusively on product regulation: facilitating entry of products into the market while limiting risks of products on health and the environment. Yet by definition, EMERs are living organisms expressly intended to be introduced and become a part of complex ecosystems over time, with potentially positive but also negative effects on biodiversity and other ecological constituents. As such, the assessments required under these product regulation regimes are much too narrow to capture the breadth of advantages and disadvantages of EMERs. Furthermore, the regulatory focus is primarily on the initial, market-entry evaluation, largely ignoring the need for ongoing monitoring of risks and adaptive management.

Lastly, the Coordinated Framework was never designed to manage the core ethical tradeoffs and goals of deploying EMERs. Indeed, the underlying statutory regimes authorizing EPA, USDA, and FDA regulation do not speak to these tradeoffs. Unfortunately, most federal conservation laws also do not allow or require consideration of the broader harms or benefits of deploying EMERs. Instead, they largely focus on either keeping things as they used to be, minimizing human intervention, or maximizing yield of a particular favored resource. Future scholarly and policy conversations must consider fundamental changes in the standards, processes, and structures of governance to more effectively promote EMERs that advance public economic and conservation goals.[1]

[1] For further elaboration of the arguments herein, see Alejandro E. Camacho & David Dana, *A Missed Opportunity to Address Ecological Risk from Emerging Biotechnologies: President Biden's Executive Order on a "Sustainable" Bioeconomy and an Agenda for Future Reforms*, 85 Ohio St. L. J. (forthcoming 2024).

Another challenge is that in many cases the important data obtained from an EMER field trial fall under confidential business information when generated by a company. This makes it difficult to incentivize the sharing of such data that would be needed to generate a reliable knowledge base about EMER properties (Box 5.2).

Box 5.2: Data Sharing and Accessibility for Risk Assessors and Managers

Christopher A. Wozniak, *Wozniak Biopesticide Consulting*

Risk assessment requires some level of background data / information to allow assessors and managers to make informed decisions about the impacts of a product of biotechnology. While qualitative risk assessment requires less data input up front as compared to quantitative risk assessment, there can be very helpful inputs which inform the qualitative assessment and enhance its accuracy. In some instances, negative data (e.g., design experiments which failed) can be informative, but are often omitted from publications and reports. For example, the DARPA Insect Allies program relied in part on construction of transgenic viruses capable of circulation, proliferation, and transmission through an insect system (e.g., aphid). When such constructs fail due to construct loss or DNA/RNA rearrangements within the vector organism, the timing and details of such a loss of function are of value to assessors in that persistence in the environment is a key parameter in understanding exposure to non-target organisms. Metabolic costs of expressing a transgene have often been assumed to lead to a return to wild type via gene loss, a notable event from an environmental risk assessment perspective. Data and detailed evidence for this phenomenon are typically lacking.

Public release of information from experimental field trials is usually redacted heavily to preclude release of Confidential Business Information (CBI), the definition of which often varies with the statute providing oversight for the technology or product. Unfortunately, some statutes and offices (i.e., Toxic Substances Control Act; EPA-Office of Pollution Prevention and Toxics (EPA-OPPT)) are notably opaque in their disclosure of any useful information regarding field trials of “new” (intergeneric) microorganisms and go beyond the usual scope of CBI as compared to other agencies/offices. The scientific community suffers from this lack of transparency and in effect recreates the wheel by experimenting without the value of some prior knowledge of an organism for a specific task (e.g., remediation of soil contaminants). How is it that EPA’s Office of Pesticide Programs publishes results on their websites or in the Federal Register of toxicological and pathology studies as well as basic details of intent or purpose of a genetic construct for microbial pest control agents, yet EPA-OPPT does not? EPA-OPP responds to FOIA requests regarding information garnered during the regulatory process for pesticides, yet EPA-OPPT does not provide even basic information about species field tested following a FOIA request for details.

In addition to the scientific community missing out on information (non-CBI) that may arise from publication of field test data or basic parameters, the public also misses out. Some statutes have “right to know” clauses which are intended to inform the public about what has been approved for release into the environment. The Toxic Release Inventory has provided information to the public regarding the movement and release of 654 specific chemicals when used at certain volumes; why does this approach not apply to release of novel microorganisms? EPA and industry have sought to weaken the disclosure of chemicals under the TRI under the guise of homeland security, however, some states have their own requirements for disclosure.

5.3: Current and emerging efforts towards updating EMER regulation

Many of the challenges towards EMER regulation are shared with the broad challenges of biotechnology regulation in an era of rapid technological advancement. As such, various groups have called for efforts to address challenges such as inter-agency coordination and jurisdictional overlaps within the Coordinated Framework, notably the White House itself through the recent Executive Order 14081 issued in September 2022 [38].

In response to the Executive Order and other calls, the regulatory agencies have initiated efforts to address many of the challenges through means that are under their authority. In this section we describe some of these ongoing efforts.

USDA's SECURE Rule: A case study in updating biotechnology regulation

Federal agencies such as USDA have in recent years begun rethinking their approach to regulating biotechnology products. including engineered microbes. In 2020, USDA released the first significant revision to its Animal Plant Health Inspection Services (APHIS) regulations since 1987.

The revised regulations, collectively termed the Sustainable, Ecological, Consistent, Responsible, Efficient (SECURE) Rule, prioritize a risk-based assessment approach, meaning that regulatory oversight is proportionate to the potential risks posed by the engineered organism. Although the SECURE Rule only covers the regulation of engineered plants, the changes they describe are useful in illustrating USDA's mindset towards modernizing biotechnology regulation more broadly.

One important feature of the SECURE Rule was to update the regulatory trigger for determining whether an engineered plant would be regulated. Previously, an engineered plant was subject to regulation if a plant pest, or genetic material from a plant pest, was used as part of the process of engineering the plant. Because many common laboratory methods for introducing genetic material into plants involve using the plant pest *Agrobacterium* as a delivery vector, many products were subject to regulation even when they were very low risk. In contrast, a potentially high-risk product could have avoided regulation as long as it was not developed using plant pests or their genetic material. The SECURE Rule updated this regulatory trigger to a more risk-based formulation, such that now an engineered plant is subject to regulation if it is itself a plant pest or poses a plant pest risk, if it contains genetic sequences that encode a compound that could cause plant disease, or if the plant is intended to create a product for pharmaceutical or industrial use [39].

The SECURE Rule also defined exemptions from regulation for certain categories of engineered plants, mostly focusing on plants containing a genetic modification that could have been achieved through conventional breeding techniques. Importantly, USDA also established an exemption for products containing the same combination of plant, trait, and mechanism of action as a previously assessed product that was found to not be subject to regulation. USDA maintains a public list of such combinations that developers can consult to help determine whether their product will be regulated [39]. Such an approach enables regulators to allocate resources effectively while ensuring appropriate oversight.

The revised regulations also emphasize consultation and engagement with stakeholders, including researchers, developers, industry representatives, and the public. This collaborative approach allows for feedback on regulatory processes, guidance documents, and risk assessments, facilitating informed decision-making.

The updated regulatory framework described by the SECURE Rule is expected to accelerate innovation in the U.S. plant biotechnology sector, particularly by lowering the regulatory burden for product development to small businesses and academics [39]. Many of the challenges with regulating plant biotechnology that were addressed by these updates, such as the existence of regulatory triggers misaligned with scientific understanding of risk, are also challenges for the regulation of EMERs. Addressing them through similar regulatory reform would likely lead to similar advances in innovation in this field.

A joint report by the USDA, EPA, and FDA on coordinating biotechnology regulation

In May 2024, the USDA, FDA and EPA announced a plan to modernize, simplify and enhance their regulations and oversight mechanisms for biotechnology products [40]. The plan, developed in response to Executive order 14081, will focus on five different topic areas, one of which encompasses EMERs.

Specifically, the plan lays out an intent for the EPA and USDA to clarify and potentially align their respective regulatory roles, processes, and requirements concerning the environmental release of modified microbes. The goal will be to minimize regulatory overlap, streamline risk assessment procedures, and improve communication between agencies, especially regarding small-scale field trials. Key actions include identifying

avenues for sharing product information, aligning application requirements and review timelines, harmonizing regulatory exemptions, exploring opportunities to minimize regulatory redundancy, and improving interagency communication through updates to their Memorandum of Understanding (MOU) on modified microorganisms. The plan also sets a schedule for formally updating the Coordinated Framework by December 2024.

In addition, USDA and EPA stated agency-specific goals including:

- USDA will clarify which modified microorganisms are subject to regulation under its authority.
- USDA will explore mechanisms to exempt certain modified microorganisms from its regulations.
- USDA will explore regulatory pathways to commercialization for non-plant organisms subject to USDA's biotechnology regulations.
- USDA will streamline its permitting process and update its user guides. One goal is to enable efficient movement of modified microbes between APHIS-approved containment facilities for contained research activities.
- EPA will explicitly support the development of biopesticides over conventional chemical pesticides, by providing technical assistance to developers, working with state pesticide agencies to streamline their deployment, and prioritizing biopesticides for regulatory review.

The report also describes plans by USDA, EPA, and FDA to work together to enable more regulatory clarity to developers through the web. These include a pilot project for a web-based tool to guide product developers in determining which regulatory agencies might regulate a particular type of product, as well as a modification to the Unified Website for Biotechnology Regulation [2] that allows developers to easily and voluntarily submit basic information about a potential product and request a meeting with all three regulatory agencies.

Efforts in Congress: The National Security Commission on Emerging Biotechnology

Legislative efforts are also currently underway in Congress to address many of the salient challenges facing EMER regulation. The National Security Commission on Emerging Biotechnology (NSCEB), established in December 2021, has been a forerunner in many of these efforts, as described in their recent interim report [1]. Although the commission was established to focus on national security, it has rightfully identified EMERs as an important component of a larger biotechnology strategy for the United States. In particular, they have endorsed the Plant Biostimulant Act, which was formally introduced to Congress in March 2023. This bill would establish a federal definition for plant stimulants, and exempt them from current regulations that pertain to plant pesticides. Plant biostimulants are a major application area for EMER technology, and defining new regulatory pathways that are better aligned with the nature of their usage will be an important step towards developing more rigorous and streamlined regulatory pathways for EMERs.

The NSCEB has also recognized the importance of clarifying, managing, and strengthening the ways in which the three main federal regulatory agencies of the Coordinated Framework jointly regulate biotechnology products, including EMERs. To this end they have drafted a number of bills, including the Agriculture Biotechnology Coordination Act, which would establish an office of biotechnology policy within the USDA to help coordinate efforts between itself and other agencies, and the Biotechnology Oversight Coordination Act, which would establish a formal coordination committee for biotechnology products. Both of these bills were formally introduced to Congress in May 2024.

A complementary approach: voluntary regulation

In addition to policy and legislative efforts from the federal government, there are also efforts from EMER developers themselves to develop voluntary, self-imposed regulatory standards for the industry (Box 5.3). Such efforts have distinct advantages and disadvantages from formal government regulation, and can serve as important complementary efforts towards ensuring EMER safety and effectiveness.

Box 5.3: Voluntary Frameworks for EMER Safety: A Valuable Tool to Strike the Appropriate Balance Between Safety and Innovation

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The goal of EMER regulation is to create the right balance of safety and innovation. Government regulations, while essential, often struggle to keep up with technological advancements or result in excessive requirements. This can be costly in both time and money, especially to smaller or early-stage companies. Unfortunately, government agencies can also struggle to obtain the resources needed to review and enforce these regulations efficiently, causing delays that discourage innovation. A voluntary, industry-driven framework to supplement government agency requirements offers an adaptable, dynamic, and feasible solution for the safe regulation of EMERs. Historically there are many examples of effective voluntary frameworks that have been widely adopted, such as ISO and ASTM industry standards, B Corp certification for companies with commitments to ethics and sustainability, and LEED certification for environmentally responsible building design. A voluntary framework can also be effective for EMER safety, as guidelines can be quickly updated to keep pace with new technologies, easing the burden on government bodies to create comprehensive regulations all at once. This adaptability enhances the effectiveness of regulations and may serve as a test case for future government mandates. Companies that collectively generate and voluntarily adopt high safety standards show a commitment to safety and transparency, which presents an opportunity to build more public support than through mandatory regulations alone. This public support is essential for the broader acceptance of EMERs in the future. A voluntary approval system that fosters trust can also be marketed to consumers, creating incentives for companies to comply with the framework. As a starting point, we envision a framework that includes standards of transparency, systematic safety assessments, ecological risk evaluation requirements, and accessibility to resources to scientifically gauge the safety of a proposed EMER. We also advocate for upfront guidance so companies can proactively assess the safety of a proposed product. For a voluntary framework to be successful we need to reasonably mitigate risk while minimizing the burden, making the standards achievable, and aligning the goals with industry motivations.

Chapter 6: Conclusions and Future Outlook

To summarize the major challenges of regulating EMER products under the current U.S. biotechnology regulatory framework:

1. **The multi-agency nature of the Coordinated Framework creates areas of jurisdictional overlap and regulatory gaps, in which EMERs can frequently fall.** This adds significant complexity, time, and resource requirements to the regulatory process, hampering innovation in the EMER sector. These additional burdens are particularly damaging to small developers of EMER products.

2. **Existing regulatory triggers, when applied to EMER products, are sometimes misaligned with current scientific understanding of the products' risks.** This can lead to cases where regulatory requirements are overly strict for a relatively benign product like a genetic reporter for tracking microbial dispersion. This could also lead to cases where regulatory requirements might be too lenient. Both cases can hamper the development of the EMER sector and erode public trust in EMER products.

3. **The scientific knowledge base for the environmental impact of EMERs is still underdeveloped.** Insights about the dispersal and persistence of EMERs and their genetic material in natural environments are a particularly important area of focus. The regulatory requirements for conducting academic field research on EMERs, as well as the difficulty in accessing existing EMER-related field trial data from proprietary sources, both contribute to this challenge.

While efforts are being taken by the federal government and by other groups to address these challenges, further reform of the biotechnology regulatory system is needed to fully resolve these issues. An appealing feature of focusing such regulatory reform on EMERs is that they parallel many of the challenges that the broader space of emerging products of biotechnology will also face in the coming years. As biotechnology advances to make new classes of unconventional products possible, these products will also face challenges such as jurisdictional overlap and regulatory gaps, misaligned regulatory triggers, and an underdeveloped scientific knowledge base. As such, pilot efforts aimed at resolving the regulatory challenges for EMERs will yield important insights that can serve as the basis for wider reform of U.S. biotechnology regulation.

Limitations of this report

Even after limiting the scope of this report to EMERs, there are still many important aspects of EMER development, regulation, and usage which have not been fully discussed in this report. For example, this report and its recommendations are focused on federal regulations, centering specifically around the EPA, USDA, and FDA. The roles of other federal agencies such as FWS and NMFS, as well as those of state-level regulatory agencies, are also an important part of EMER regulation and deployment which this report does not discuss in detail. Additionally, this report places a strong emphasis on pre-market regulation and oversight. Postmarket oversight can play an equally important role in regulating and shaping the development of a technology sector, and proper oversight of EMERs will likely face unique challenges compared to other types of biotechnology products in this domain as well. Finally, the importance and challenge of accounting for the inputs of various publics at multiple steps along the pipeline of product development and commercialization has not been discussed. Because EMERs will be released into the wider environment, they have the potential to impact wide-ranging groups of people in multifaceted ways, which will compound the importance of creating reliable channels by which potentially impacted groups can provide input into the process.

We recognize the limitations of this report by acknowledging that it is just a first step in our contribution to the wider discussion around EMER development and regulation. In particular, this report was written based on conversations based out of a single workshop. The specific makeup of the workshop's participants and their backgrounds and expertises shaped the nature of the conversations that occurred, and other reports based on other workshops may yield different insights about how best to resolve the challenge of regulating EMERs. We therefore encourage further discussions on this topic in government, industry, academic, and wider public spaces.

Chapter 7: Policy Recommendations

Building on the challenges and opportunities presented in the earlier chapters, in this chapter we make specific recommendations regarding changes to regulatory policy that could address some of these opportunities and challenges. The recommendations here are the results of numerous discussions by the editors of this report and it should not be assumed that any particular participant in the workshop that led to this report has endorsed any particular recommendation made in this chapter.

The recommendations presented here address two major challenges:

- Consistency and clarity in EMER regulation (Recommendations A, B, F)
- Enabling a scientific knowledge base for EMERs (Recommendations C, D, E)

Many of these recommendations involve the creation of new government entities and/or statutory change, and many of the specific details associated with their implementation will need to be made concrete through additional discussions by the relevant parties. Our goal in presenting these recommendations is to introduce and emphasize the importance of the ideas therein to the larger dialogue around modernizing the U.S. regulatory framework for engineered microbes and, more specifically, EMERs.

A. A Regulatory Guide for Small EMER Developers

Background:

Navigating the U.S. regulatory framework for biotechnology is a daunting challenge for small developers with little experience in this space. The consequences of minor differences in product specification and use intent, particularly for EMERs as they can often lie within the jurisdiction of all multiple agencies, can have major consequences on the time and nature of the product's regulatory assessment. An entity to explicitly help shepherd EMER products from small developers through this process would accelerate innovation in this space.

Recommendation:

Congress should authorize and appropriate funds to establish a program, with input from regulatory and environmental agencies, to explicitly aid small / first-time EMER developers in navigating the biotechnology regulatory framework. Examples of activities include:

- Dedicated and preemptive outreach to small developers early in the product development process, while there is more flexibility about product design and intent.
- Providing representative "open public release" (OPR) data packages that demonstrate the type and depth of information that is required for submission, with the goal of having a single data package format that can be used for parallel assessment by all relevant agencies. (See also Recommendation D.)
- Funding for grants to small developers of EMER products in obtaining the data necessary for regulatory assessment should be increased. This should be accomplished both by expanding existing grants programs (like the Small Business Innovation Research (SBIR) grants [41]) to explicitly include EMER products, and by establishing new grants programs for EMER developers (e.g., following the IR-4 Project model [42]). Additional means of financial support, such as a federal loan guarantee program for small EMER developers, should also be established.

B. An Environmental Biotechnology Regulation Office

Background:

One of the major factors contributing to unpredictability in the duration and resource costs of the regulatory assessment process stems from the fact that many products lie potentially within the jurisdiction of multiple regulatory agencies, which each have different risk assessment frameworks and statutory requirements. This issue is particularly true for EMERs, as their scope of deployment is wide and multifaceted. An external entity that could quickly and authoritatively resolve such potential points of confusion could accelerate and increase the predictability of the time to a regulatory decision for a new EMER product.

Recommendation:

Congress, with input from the National Security Commission on Emerging Biotechnology (NSCEB), should authorize and appropriate funds to **establish an Environmental Biotechnology Regulation Office (EBRO) to handle biotechnology products that do not neatly fall within the purview of a single regulatory agency under the Coordinated Framework**. Such products could either lie within the jurisdictional overlap of multiple agencies or fall within a "regulatory gap" where it lies outside of the conventional remit of any single agency.

Just as DARPA can operate within the Department of Defense under a special transactional authority called the Other Transaction Authority (OTA) that allows it to bypass some federal contracting regulations to enable the speed and flexibility needed to address national security interests [43], **EBRO should operate under a "special regulatory authority" that allows it to supersede existing regulatory triggers and assign the assessment of incoming products to one or more specific agencies under specified risk assessment frameworks**. These risk assessment frameworks could come from existing statutory frameworks (e.g., FIFRA, TSCA), from Congress itself in establishing EBRO, or, consistent with the appropriate delegation by Congress of such a special regulatory authority, potentially be developed by EBRO itself.

EBRO should follow a broad set of guidelines to encourage the timely review of incoming products with a level of rigor that is commensurate with an initial qualitative risk assessment. Example guidelines include:

- Removal of regulatory distinctions between intrageneric and intergeneric products.
- A risk-based classification of microbial "chassis" strains should be developed, to help expedite future preliminary risk assessments of incoming products. The ASTM standard E3214-19 Classification for Industrial Microbes [44] could be a starting point for such a risk-based classification of EMERs.
- Low-risk products should be regulated with a similar standard to equivalent, non-biotechnological interventions.

  Example: A proposal to introduce a microbe with a benign genetic modification (e.g. a fluorescent reporter gene) into an environment should be regulated similarly to equivalent methods of non-engineered microbial introduction, such as via the transportation of soils between different environments. This may result in complete exemption of such low-risk activities from regulation.
- Adoption of conditional/tiered approval stages for products based on sequential assessments with increasingly rigorous standards.
- The earliest product approval stages (permitting the most limited release cases) should be granted under regulatory decisions that approve whole classes of similar EMER products, rather than always requiring each new product to be assessed individually.

EBRO should be housed within an existing federal body, while still maintaining its own regulatory authority (similar to a DARPA-style agency). Potential options include:

- The Office of Science and Technology Policy (OSTP), potentially via the Bioeconomy Initiative Coordination Office (BICO)
- A White House-based Initiative Coordination Office (ICO), or alternatively a council administered by ICO that includes OSTP, the Domestic Policy Council, and the Office of Information and Regulatory Affairs (OIRA).
- The newly-announced National Bioeconomy Board, which is co-chaired by OSTP, the Department of Commerce, and the Department of Defense [45].
- The Office of Information and Regulatory Affairs (OIRA)
- The National Institute of Standards and Technology (NIST)

EBRO could initially be established with a narrow remit to focus only on EMER products, wherein its impact on the regulatory assessment process for these products (with a focus on time to decision) should be tracked during an initial pilot period. Successful performance should then motivate its expansion to nonmicrobial biotechnology products intended for environmental release.

C. Public Infrastructure for Testing EMER Products

Background:

Field trials of EMERs, particularly for academic research, are currently difficult to conduct because of regulatory constraints on their execution. Pre-approved infrastructure for conducting such tests would lower the barrier to entry for EMER development and science.

Recommendations:

Congress should authorize and appropriate funds to **establish testbed infrastructure for the assessment of the performance and ecological impact of EMERs in contained conditions that simulate natural environments**. These testbeds should be accessible to both product developers and to academic researchers. Proposals for EMER field trials within these testbeds should undergo a streamlined regulatory review process due to the minimal risk of broader release from these sites.

This testbed infrastructure could fit into the Department of Energy National Laboratory architecture, either through an existing national lab or a new national lab dedicated to EMERs. Other federal entities that could contribute to or oversee this infrastructure include the Department of Defense (via BioMADE), the National Institute for Standards and Technology (NIST), the Bureau of Land Management (BLM), and/or other agencies that oversee the maintenance of terrestrial/aquatic resources.

D. A Single Point of Aggregation for EMER-related Data

Background:

A major factor that delays regulatory decisions for EMER products is the lack of wide-scale data about the behavior of engineered microbes in natural environments. Greater availability of such data would help establish precedents and expectations for EMER behavior in field trials, contributing to clear, evidence-based benchmarks for performance that can be communicated to developers prior to formal regulatory assessment.

Recommendations:

The Environmental Biotechnology Regulation Office (EBRO) should, with the support of the National Institute for Standards and Technology (NIST), **establish and maintain a publicly accessible database that contains data about EMER field trial performance** in a standardized format.

Federal and private funding agencies that support research related to EMERs should include stipulations in their grants and contracts that all federally supported field trial data must be deposited into this public repository, regardless of whether it is published in an academic journal.

Furthermore, use of the public EMER testing infrastructure (Recommendation C) for field trials should be conditioned on the agreement to deposit "noncompetitive data" into the public repository. Examples of "noncompetitive data" might include:

- Data depositions that do not become public until a fixed time elapses
- Deposition of data that pertains only to the dispersal/persistence of the microbial strain, but not the performance of its engineered function
- Deposition of data relating to products whose commercialization efforts cease (e.g., due to a later regulatory decision)

Furthermore, EBRO should oversee that the noncompetitive data from future regulatory assessments of all EMER products should be deposited into this database, making the database a **single point of aggregation** for EMER-related data. EBRO should also pursue ways to incentivize developers to publicly share noncompetitive data related to their EMER products.

E. Funding of Basic EMER-related Research

Background:

There still exist many fundamental scientific questions about the behavior of EMERs in natural environments that are unresolved. Greater insights made possible by regulatory science research can help inform the risk assessment frameworks used in regulatory decisions for EMERs and potentially expedite the regulatory process while preserving its rigor.

Recommendation:

Federal and private funding agencies should provide more **funding for basic research questions in the areas that are relevant to informed risk analyses of EMERs.**

These areas include:

- Developing **rigorous scientific definitions of potential ecosystem harm, risk, and benefit** due to an introduced microbial product.
- Determining the **principles governing the dispersal and persistence** of both engineered microbes and their DNA when introduced into various types of natural environments, particularly compared to non-engineered microbes and DNA.
- Enabling **better predictability of microbial behavior in, and impacts to, external environments** based on laboratory-scale and mesocosm-scale characterization data.

In cases where existing funding programs, such as USDA's Biotechnology Risk Assessment Grants (BRAG) program [46], can be expanded to include these research areas, such action should be prioritized.

F. Agency-Developer-Publics Communications

Background:

The lack of materials that clearly communicate the complex nature of the biotechnology regulatory framework, particularly as it applies to EMERs, is a major deterrent for both scientific and technological innovation in this space as well as public trust in EMER technology more broadly.

Recommendations:

Congress should authorize and appropriate funds to allow both federal and state-level regulatory agencies to establish and maintain **programs to promote the early and regular interaction between regulators, potential developers of EMERs, and the broader publics.** Such programs could include:

- **Dedicated citizen outreach efforts** to engage with citizen groups to solicit sentiments about EMERs, both in general and in the case of specific EMER products under review for release in a local environment.
- **A horizon scanning framework** wherein all federal research grants involving engineered microbes and environmental microbiology would prompt the recipients to report whether they believe their work could be applicable for environmental release. These responses could then be scanned to identify targets for outreach efforts from the regulatory agencies.
- **A grants program to universities and other research entities** to support the establishment of interpersonal engagement between regulators and researchers in EMER-related areas prior to the conceptualization and development of actual EMER products. (This could also be tied in with the Regulatory Guide program in Recommendation A).

Underlying all of these above recommendations is the need for further staffing and funding for the regulatory agencies themselves, without which these recommendations cannot be implemented. The EMER space, and biotechnology in general, are currently in a period of rapid advancement and regulators must be given the required resources to meet these rising demands and preempt upcoming challenges.

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