Managing Risks of Synthetic Biology: Assessing the U.S. Regulatory System Microbes Engineered for Chemical Production or Bioremediation

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Uncertainty surrounding emerging synthetic biology technology, and its attendant potential benefits and risks, will create significant challenges for the U.S. regulatory system. Regulatory systems, almost by definition are designed for technologies existing at the time of the regulatory systems' formation and are based on the then-current understanding of that technology. Unsurprisingly, regulatory systems often face difficulty and disruption when applied to newly emerging technologies.[1]

This whitepaper discusses the authority that the existing U.S. regulatory system provides the Environmental Protection Agency (EPA) concerning two particular categories of potential synthetic biology products: microbes engineered for chemical production and for bioremediation. The analysis reveals that although the extant regulatory system is capable of handling several aspects of these synthetic biology microbes sufficiently, there are also a number of potentially significant regulatory gaps. These gaps arise because synthetic biology presents particular challenges for the existing U.S. regulatory regime due to three atypical characteristics of this nascent technology: synthetic biology organisms can evolve; the traditional relationship between mass and risk may break down for synthetic biology products; and the conventional regulatory focus on end-product chemicals may be a poor match in certain instances for a technology that produces novel organisms, with their own attendant risks, that, in turn, produce the end-product chemicals. While none of these characteristics are entirely unique to synthetic biology products, the manner in which they present in this case raises certain concerns.

The challenges that the existing regulatory system faces for synthetic biology microbes produced for chemical production or bioremediation are elaborated below. The first part of the paper discusses issues that are common to both types of synthetic biology microbes; the second part focuses on issues singular to each type independently.

I. Synthetic Biology Microbe Regulation

Synthetic biology is not regulated as a particular technology per se. Rather, pursuant to the Coordinated Framework for Regulation of Biotechnology, synthetic biology is regulated based on particular products and particular uses.[2] As such, synthetic biology microbes will be regulated by the EPA pursuant to existing environmental and human health protection statutes. The primary statute governing synthetic biology microbes engineered for chemical production and bioremediation is the Toxic Substances Control Act. Other statutes, including the Federal Insecticide, Fungicide, and Rodenticide Act; Resource Conservation and Recovery Act; Comprehensive Environmental Response, Compensation and Liability Act; and Endangered

[1] *See ~~generally~~ Gregory*generally* Gregory Mandel, *Regulating Emerging Technologies*, 1 LAW, INNOVATION, & TECH. 75 (2009).

[2] Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986).

Species Act are pertinent to the regulation of synthetic biology microbes as well. The regulation of synthetic biology microbes pursuant to these laws are discussed in the following sections.

A. The Toxic Substances Control Act

The Toxic Substances Control Act (TSCA) regulates the use of hazardous chemical substances.[3] Unlike most other environmental statutes, TSCA is not limited by the medium in which the chemicals are released or the manner in which the chemicals are used, and therefore is one of the broadest environmental statutes in scope. In addition, TSCA permits regulation of chemical substances before and potentially during their use.[4] For these reasons, TSCA is likely the most important statute concerning the EPA's regulation of synthetic biology microbes engineered for chemical production and bioremediation.

1. TSCA Section 5

The most significant provision of TSCA for synthetic biology purposes is Section 5. This section authorizes the EPA to regulate hazardous chemical substances where the manufacture, processing, distribution in commerce, use, or disposal of the substance presents an unreasonable risk of injury to health or the environment.[5] Where a chemical substance presents an unreasonable risk, the EPA may prohibit or limit the amount of its manufacture or use.[6] "Chemical substance" is defined broadly under TSCA to include "any organic or inorganic substance of a particular molecular identity, including—(i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature and (ii) any element or uncombined radical."[7] Microbes engineered through synthetic biology are organic substances, and EPA has concluded that living microorganisms are chemical substances under TSCA.[8]

Pursuant to TSCA, the EPA maintains the TSCA Chemical Substance Inventory (TSCA Inventory), a list of existing chemical substances that have been approved for manufacture and processing in the United States.[9] A chemical substance listed on the TSCA Inventory may be manufactured and used unless the EPA finds that it poses "an unreasonable risk of injury to health or the environment," which is defined as a risk that is not outweighed by the benefits of the chemical substance.[10] A party may not, however, manufacture or use a "new chemical

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3 15 U.S.C. §§ 2601–95d (2000).
4 *See* 15 U.S.C. §§ 2601–92.
5 *Id*. § 2605.
6 *Id*.
7 *Id*. § 2602(2)(A).
8 This conclusion could be challenged on the basis that living organisms do not have "a particular molecular identity," but it is likely that EPA's interpretation would be upheld. *See* Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984) (establishing judicial deference to agency's reasonable interpretation of ambiguous statutory language).
9 15 U.S.C. § 2607(b); 40 C.F.R. § 712.30 (2007).
10 15 U.S.C. § 2604(b)(2)(B)(i).

substance" or place a TSCA Inventory substance into a "significant new use" without premanufacture notification (PMN).[11]

EPA has issued a final rule stating that intergeneric microorganisms, which are defined as "organisms formed by combining genetic material from organisms in different genera," are new chemical substances under TSCA.[12] Thus, microbes engineered for chemical production or bioremediation generally would be considered new chemical substances under TSCA and subject to TSCA's premanufacture notice requirements. Intergeneric organisms are governed by special premanufacture notice requirements, termed the Microbial Commercial Activity Notice (MCAN).[13] The MCAN requirements are generally similar to conventional PMN requirements, with some differences noted below.

Synthetic biology, as opposed to traditional genetic modification, raises the possibility of introducing wholly synthetic genes or gene fragments into an organism. Similarly, synthetic biology may allow scientists to remove a gene fragment from an organism, modify that fragment, and then reinsert it back into the same organism. In either case, such organisms may not be "intergeneric" under the current regulatory definition because they would not include genetic material from organisms of different genera. The regulatory status of non-"intergeneric" genetically modified microorganisms is unclear. The MCAN regulations state that they "establish[] all reporting requirements [for] microorganisms,"[14] which indicates that non-intergeneric genetically modified organisms may not be covered by any TSCA premanufacture notice requirements. Alternatively, the regulations might be interpreted to indicate that such organisms are covered by TSCA's conventional PMN requirements, as opposed to the MCAN requirements. Separate concerns are raised under either scenario.

Where premanufacture notification is required, notice must be given to the EPA at least ninety days before manufacture or processing of the new substance or engaging in the new use.[15] The notice must include known and reasonably ascertainable data that the applicant believes shows that the new chemical substance or new use of an existing chemical substance "will not present an unreasonable risk of injury to health or the environment," and such data must be made available for examination by interested persons.[16] There is no requirement that the manufacturer provide any particular types of data or develop any particular data, only that the manufacturer provide whatever data already exists. EPA then has ninety days to review the submission in order to determine whether the new chemical substance may present an unreasonable risk. Given the lack of particular data requirements and EPA's limited knowledge concerning potential synthetic biology microbe risks, it may be difficult or impossible for EPA to adequately assess the pertinent risks within ninety days. Intergeneric microorganisms used in research and

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[11] 15 U.S.C. § 2604(a)(i). The significant new use rules are subject to different procedural requirements than the new chemical substance rules, but provide the EPA with essentially the same substantive authority. 15 U.S.C. § 2604(a)-(b). It is expected that engineered microbes will, at least initially, primarily present new chemicals as opposed to new uses.

[12] 40 C.F.R. §§ 725.1(a), 725.3.

[13] 62 Fed. Reg. 17,190 (Apr. 11, 1997).

[14] 40 C.F.R. §§ 725.1(a).

[15] *Id*. If EPA takes no action within 90 days, manufacture of the chemical may proceed. *Id.* § 2604(b)(i).

[16] *Id*. § 2604(b).

development for commercial purposes that are going to be released into the environment require a TSCA Experimental Release Application (TERA), which must be submitted at least sixty days prior to field trials.[17] As with the ninety-day premanufacture notice window, sixty days may not be enough time for EPA to adequately evaluate the novel risks presented by synthetic biology microbes. In certain circumstances, the EPA may be able to "stop the clock" while waiting to receive additional information that it has requested from an applicant, which may ameliorate some of the timing concerns.

If the EPA has a "reasonable basis" to conclude that a substance may present an unreasonable risk of injury to health or the environment, it may prohibit or limit the amount of the substance's manufacture or use.[18] Alternatively, the EPA may allow the chemical substance to be used subject to certain use restrictions, or allow manufacture and use without limitation.[19] Because the burden of proof of establishing a reasonable basis is on the EPA, reaching a finding of an unreasonable risk to health or the environment for synthetic biology microbes, particularly within this limited time frame, will be a significant challenge, especially in the early stages of synthetic biology development, as the data and understanding concerning synthetic biology risk analysis are lacking or are limited. In many cases, it may be impossible to understand certain synthetic biology microbe risks well until the technology develops further.

Alternatively, the EPA may require testing with respect to health and environmental effects if a chemical substance is going to (1) be produced in substantial quantities and (2) will either "enter the environment in substantial quantities" or produce "significant or substantial human exposure."[20] Because the substantial quantity measures are set by statute and regulation based upon traditional chemical quantities and a direct relationship between mass and risk, these thresholds are likely inappropriate for synthetic biology microbes. It is likely that for many synthetic biology microbes engineered for chemical production and bioremediation the EPA will both lack a reasonable basis to conclude that the microbes present an unreasonable risk of injury to health or the environment and that production of the microbe will fall below the quantitative production threshold. In these cases, the EPA lacks statutory authority to require further testing concerning human health and environmental impacts. In general, EPA will have a very difficult

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[17] 40 C.F.R. §§ 725.3, 725 Subpart E. Intergeneric microorganisms used for research and development in contained structures are exempt from MCAN and TERA reporting requirements. 40 C.F.R. § 725.234. There are additional exemptions from MCAN and/or TERA reporting requirements as well. *See* 40 C.F.R. §§ 725.205 (exempting microbial pesticides manufactured solely for research and development from MCAN and TERA requirements), 725.238 & 725.239 (exempting research and development testing of specific microorganisms under certain conditions from MCAN and TERA requirements) , 725.505 (exempting test marketing activities with no unreasonable risk of harm from MCAN requirements), 725.424 & 725.428 (exempting specific microorganisms from MCAN requirements under certain containment conditions).

[18] *Id*. § 2603(e)(1)(A).

[19] *Id*. §§ 2603(c), 2604(h).

[20] *Id*. § 2603(a)(1)(B)(i). The substantial production threshold is "1 million pounds, aggregate production volume of the substance per year for all manufacturers"; the substantial release threshold is "1 million pounds of release to the environment from all sources per year; or release equal to or greater than 10 percent of production volume per year, whichever is lower." 15 U.S.C. § 2603(a)(1)(B); Final Statement of Policy, 58 Fed. Reg. 28,736, 28,746 (May 14, 1993). "[S]ignificant or substantial human exposure" is roughly defined as exposure of 100,000 people in the general population, or less where a subpopulation is exposed more directly or on a routine or episodic basis. *Id*. Lower figures apply for the exposure of consumers of the substance or persons who work with the substance. *Id*.

role to play under TSCA in balancing the need to conduct adequate risk assessments with the desire of the synthetic biology industry and other members of the public to develop this nascent technology.

In addition to these broad limitations, there are several exceptions in TSCA that raise particular concerns with respect to synthetic biology microbes. Chemical substances used in research and development that are not manufactured for "commercial purposes" are exempt from TSCA's premanufacture notice requirements.[21] "Commercial purpose" is defined broadly by the EPA under TSCA to include the any production of chemical substances with the purpose of obtaining an immediate or eventual commercial advantage.[22] This definition specifically includes research and development activities with a commercial purpose.[23] Private, non-"commercial purpose" activities, however, are beyond TSCA's scope.[24] As many expect synthetic biology to popularize and decentralize the development of new organisms,[25] this presents a significant gap in the regulation of synthetic biology microbes. EPA has attempted to define "commercial purposes" as broadly as possible,[26] but the definition does not reach all expected synthetic biology activities, and the definition itself may be subject to statutory or constitutional challenge on its breadth. As one example, the International Genetically Engineered Machine (iGEM) competition is an annual synthetic biology competition that involves thousands of undergraduate students building biological systems out of a set of biological parts. Because this or similar competitions may not involve a "commercial purpose," the engineered microbes developed as a part of such activities may not be subject to TSCA. Though this potential gap is pertinent to other technologies as well, synthetic biology is expected to enable more widespread non-commercial research than many other fields involving the development of chemical substances.

In addition to this general exception that could apply to any synthetic biology microbe, additional exemptions could potentially apply to synthetic biology microbes that are not subject to the MCAN requirements because they do not fall within EPA's current definition of intergeneric microorganisms.[27] To the extent traditional PMN requirements are considered to apply to such microbes, there are two exemptions to standard PMN requirements of potential concern here. First, chemicals made in quantities of less than 10,000 kilograms are largely exempt from TSCA regulation.[28] Because limited amounts of synthetic biology organisms (i.e., less than 10,000 kilograms) could be used to produce large quantities of TSCA Inventory chemical product, situations where a new synthetic biology organism is producing an already

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[21] 40 C.F.R. § 720.22(a)(1); *see also* 40 C.F.R. § 725.234 (providing an exemption from TSCA Experimental Release Application requirements for certain enclosed research and development activities).

[22] 40 C.F.R. § 720.3(r).

[23] *Id.*

[24] Presidential Commission for the Study of Bioethical Issues, NEW DIRECTIONS: THE ETHICS OF SYNTHETIC BIOLOGY AND EMERGING TECHNOLOGIES 94 (2010); Michael Rodemeyer, *New Life, Old Bottles*, SYNTHETIC BIOLOGY PROJECT 23 (2009), *available at* http://www.synbioproject.org/library/publications/archive/synbio2..

[25] *See* National Science Advisory Board for Biosecurity, ADDRESSING BIOSECURITY CONCERNS RELATED TO SYNTHETIC BIOLOGY ii-iii (2010).

[26] *See* 40 C.F.R. § 725.205.

[27] *See supra* page 3.

[28] *See, e.g.*, 40 C.F.R. § 723.50 (2007). Such chemicals still require a 30-day notice. 40 C.F.R. § 723.50(a)(2)(i).

approved chemical substance may escape substantive TSCA oversight. There is an exception to the 10,000 kilogram exemption if the chemical may cause serious acute, chronic, or significant environmental effects, but the EPA has the burden of establishing such a risk.[29] The 10,000 kilogram exemption, like many environmental standards, is premised on a direct relationship between mass and risk, a relationship that may break down for genetically modified microbes, including those created using synthetic biology.

Second, chemical substances with low environmental releases and human exposures are also largely exempt from TSCA's standard PMN requirements.[30] The low environmental release exemption was developed with traditional chemical substances in mind, substances that cannot proliferate. Synthetic biology microbes, like other living substances, may be able to reproduce. A limited release of synthetic biology microbes could proliferate in the environment into a significant concern. EPA has faced a similar concern with genetically modified microbes developed using traditional genetic engineering techniques. In those circumstances, the EPA relied on the presumption that the basic biology of the specific microbe had not changed as well as monitoring and field testing for persistence and competitiveness with indigenous species. The presumption concerning basic biology will less applicable to various synthetic biology microbes, and careful field testing and monitoring will be necessary. There is also a concern that synthetic biology microbes produced and maintained in contained environments may qualify for the low release/law exposure exemption,[31] even as they are used to produce substantial amounts of TSCA Inventory chemicals.

The technology of synthetic biology may interact with these exemptions in ways that raise additional challenges under TSCA. In particular, because synthetic biology involves the manufacture of new organisms themselves designed to produce chemical products, TSCA may be a poor fit in certain regards. Where the product produced by a synthetic biology microbe is itself a new chemical substance, TSCA will apply in roughly its traditional manner, subject to the issues discussed here. Where, however, a new synthetic biology microbe is intended to produce an already listed TSCA Inventory chemical substance, new concerns arise. If the synthetic biology microbe is subject to the low volume or low release/exposure exemption, for example, the microbe may not receive review, even though it may be used to produce substantial amounts of chemical substances. Although the chemical products are intended to be identical to TSCA Inventory substances, one of the hallmark characteristics of organisms is that they evolve. A synthetic biology microbe thus may mutate to produce non-Inventory chemicals, without the manufacturers' knowledge. These new chemical products could have different risk profiles from the intended chemical product. Microbes may be able to be designed so that the risk of evolution is low, and manufacturers could monitor their output products voluntarily, but TSCA generally does not require this. In addition, because the initial microbe was not subject to TSCA requirements, it may not have been appropriately evaluated in the first instance for risks related to evolution or other concerns.[32]

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[29] 40 C.F.R. § 723.50(d).

[30] 40 C.F.R. § 723.50.

[31] Regulations define the requirements for contained environments. 40 C.F.R. § 723.50(c)(2).

[32] It is possible that there have already been genetically modified microbes produced through traditional rDNA techniques that raise similar issues, but there does not appear to be any publicly available information on such.

Where a synthetic biology microbe is not subject to premanufacture notification requirements because it is not a new chemical or a new use, the EPA still has authority pursuant to TSCA's existing chemical substances regulations to review any potential health or environmental concerns and to regulate the substance if it presents "an unreasonable risk of injury to health or the environment."[33] Exercise of such authority, however, requires that the EPA engage in a cost-benefit analysis based on the effects of the chemical substance on human health and the environment, the benefit of the chemical substance, the availability of substitutes, and the economic consequences of any limitation.[34] This standard has proven difficult to meet—in fact, the EPA has not tried to exercise this authority since a proposed ban on most asbestos products, based on ten years of study and a 45,000 page record, was struck down by a federal circuit court in 1991 for lacking sufficient cost-benefit analysis and not imposing the least burdensome regulation.[35] For these reasons, TSCA (or the judicial interpretation of TSCA) has been criticized by commentators for imposing unrealistic data and certainty requirements.[36] Considering the limited scientific knowledge concerning the risks of synthetic biology microbes, it would be difficult, if not impossible, for EPA to conduct the necessary cost-benefit analysis to satisfy the least burdensome regulation requirement here.

2. TSCA Sections 4 and 6

TSCA Section 4 permits EPA to require manufacturers of listed chemical substances to conduct tests "to develop data with respect to the health and environmental effects" of the substance.[37] EPA may require such testing if it determines that the chemical substance either may present an unreasonable risk to human health or the environment and that there is insufficient data for a chemical for which there will be substantial human or environmental exposure.[38] These provisions, however, require notice and comment rulemaking, and therefore are very cumbersome. Due to the current scientific uncertainty surrounding synthetic biology, it would likely be some time before EPA is able to meet the evidentiary standards required. More realistically, EPA may be able to use Section 4 in combination with Section 5's premanufacture notice requirements to pressure manufacturers into consent decrees to develop the necessary data that EPA needs to assess risk or to implement certain safety measures.

As the foregoing overview reveals, one of the most concerning limitations of TSCA for the management of synthetic biology organisms is the lack of any effective post-commercialization reporting requirements or mechanism. Once a chemical substance is listed in the TSCA Inventory, EPA generally does not require a manufacturer to provide any data on the uses or

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[33] 15 U.S.C. § 2605(a).

[34] *Id.*

[35] *See* Corrosion Proof Fittings v. EPA, 947 F.2d 1201, 1215–16 (5th Cir. 1991) (striking down EPA's final rule asbestos ban).

[36] Albert C. Lin, *Size Matters: Regulating Nanotechnology*, 31 HARV. ENVTL. L. REV. 349, 361–67 (2007) (discussing critiques of TSCA).

[37] 15 U.S.C. § 2603(a) (2000). This includes the ability for EPA to use this authority to develop data for other agencies. *Id.* § 2603(e).

[38] *Id*. § 2603(a)(1)(A).

properties of a substance.[39] Though this is a challenge that confronts all chemical substances under TSCA, it is a particular concern for synthetic biology microbes engineered for chemical production or bioremediation because such microbes can evolve. Without regular monitoring of the microbes and their products, it will be impossible to know whether they have mutated to produce products that represent new risks to human health or the environment. Beyond these concerns about direct risks to human health or the environment, post-commercialization data and information would also be particularly beneficial to gather in the early stages of synthetic biology development and risk assessment for both agencies and scientists to advance their understanding of this technology. EPA would benefit from substantially stronger data-gathering authority under Section 4, particularly post-commercialization, for understanding synthetic biology microbe evolution and fate.

TSCA Section 6 authorizes EPA to regulate the manufacture, processing, and use of a chemical substance where there is a reasonable basis to conclude that the substance "presents or will present an unreasonable risk of injury to health or the environment."[40] This includes the authority to prohibit or limit chemical production, and to require labeling and notification pertaining to the chemical.[41] Section 6 actions, however, must also be accomplished through notice and comment rulemaking based on a finding of unreasonable risk, a standard that EPA would likely be unable to meet for the foreseeable future with respect to synthetic biology microbes.[42] Again, EPA's authority under TSCA once a chemical is listed is very limited.

B. RCRA and CERCLA

In addition to TSCA, both the Resource Conservation and Recovery Act and the Comprehensive Environmental Response, Compensation and Liability Act are pertinent to the regulation of synthetic biology microbes engineered for chemical production and bioremediation.

1. The Resource Conservation and Recovery Act

The Resource Conservation and Recovery Act (RCRA),[43] which amended the Solid Waste Disposal Act,[44] regulates the generation, transportation, management, and disposal (other than to surface water) of solid and hazardous wastes.[45] A waste is subject to RCRA's requirements if it has been listed by EPA or if it exhibits certain hazardous characteristics, such as would pose a threat to human health or the environment.[46] RCRA also contains groundwater monitoring and

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[39] TSCA does require manufacturers to report information where new information "reasonably supports the conclusion that [a chemical substance] presents a substantial risk of injury to health or the environment." 15 U.S.C. § 2607(e).

[40] 15 U.S.C. § 2605(a) (2000).

[41] 15 U.S.C. § 2605(a) (1)-(7) (2000).

[42] In addition, TSCA Section 7 permits EPA to initiate a civil action to seize an immanently hazardous substance. 15 U.S.C. § 2606(a).

[43] Pub. L. No. 94-580, 90 Stat. 2,795 (1976).

[44] 42 U.S.C. §§ 6901–92k (2000).

[45] 40 C.F.R. pts. 260–79 (2007).

[46] *Id*. § 261.3; 42 U.S.C. § 6903(5).

corrective action requirements that apply to hazardous waste releases.[47] Synthetic biology microbes engineered to produce chemical products or for bioremediation that meet the definition of RCRA hazardous wastes will be subject to RCRA's disposal and other requirements.

EPA's current system for regulating generators of solid and hazardous waste under RCRA may raise concerns for synthetic biology. RCRA requirements for generators vary based on the mass of hazardous waste generated. "Large quantity generators," for example, have more stringent notification, contingency plan, and waste storage requirements than "small quantity generators" and "conditionally exempt small quantity generator[s]."[48] Because the toxicity of a synthetic biology microbe may not bear the same relation to mass as for traditional waste, the EPA's current classification scheme for RCRA waste generators may not be appropriate for synthetic biology products.

2. The Comprehensive Environmental Response, Compensation and Liability Act

The Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) provides a system of remediation and liability for releases of hazardous materials that pose a risk to human health and the environment.[49] CERCLA liability and enforcement authority generally turns on whether a release involves a "hazardous substance," a term defined broadly under the statute.[50] The EPA has the authority to include any substance that "when released into the environment may present substantial danger to the public health or welfare or the environment."[51] To the extent a synthetic biology microbe is identified as hazardous or presents hazardous characteristics, it will be subject to CERCLA's requirements if there is a release. CERCLA provides substantial authority to remediate a hazardous release, but by definition is a reactive, not proactive, tool, and therefore is of little assistance except as a deterrent measure in preventing problematic synthetic biology releases.

C. Risk Assessment Challenges

As indicated by the discussion above, EPA's ability to adequately regulate synthetic biology microbes engineered for bioremediation or chemical production will be substantially dependent on EPA's ability to assess the risks of new synthetic biology organisms. This is an extremely daunting task. Currently, EPA generally evaluates the risks of a new organism based upon the known relatives of that organism.[52] This method may be insufficient for synthetic biology microbes, given that such microbes may be derived from a large number of existing organisms,

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47 40 C.F.R. §§ 264.92–.101; *see also* U.S. ENVTL. PROT. AGENCY, OFFICE OF SOLID WASTE, RCRA GROUND-WATER MONITORING: DRAFT TECHNICAL GUIDANCE (1992), *available at* http://www.epa.gov/correctiveaction/resource/guidance/sitechar/gwmonitr/rcra_gw.pdf. A chemical substance listed on the TSCA Inventory or registered pursuant to FIFRA can also be a RCRA hazardous waste, and would then be subject to both statutes' requirements.

48 40 C.F.R. § 261.5; *see also* U.S. ENVTL. PROT. AGENCY, MANAGING YOUR HAZARDOUS WASTE 3 (2001), *available at* www.epa.gov/epaoswer/hazwaste/sqg/handbook/k01005.pdf.

49 *See* 42 U.S.C. § 9601 (2000 & Supp. 2004).

50 *Id*. § 9607(a), 9601(14) (2000).

51 *Id*. § 9602(a).

52 Presidential Commission on Bioethical Issues, *supra* note 24, at 131; Rodemeyer, *supra* note 24, at 26.

with no particular organism providing a close enough relative for pertinent risk assessment purposes. As noted above, a significant manner in which the EPA has evaluated traditionally genetically engineered microbes depends on the presumption that the basic biology of the microbe had not changed though genetic engineering. This presumption may not be true for a variety of synthetic biology microbes. Even a synthetic biology microbe that may be similar to an existing organism in many ways could contain significant differences with unknown effects on risk. These risks will be exacerbated for any microbe released into the environment, given the uncertainty of the organism's interaction with various external environmental stimuli. Risk assessment for synthetic biology is in its infancy, raising substantial challenges for much of EPA's analyses.[53]

II. Synthetic Biology Microbes Engineered for Chemical Production or Bioremediation

In addition to the regulatory concerns discussed above that are common for synthetic biology microbes produced for chemical production and for bioremediation, there are additional regulatory concerns with respect to each of these types of synthetic biology products.

A. Bioremediation Product Concerns

1. Intentional Release into the Environment

Synthetic biology microbes engineered for bioremediation raise particular concerns because of the intentional release of synthetic organisms into the environment. Synthetic biology microbes released into the environment could mutate or interact with other organisms and the environment in unexpected ways leading to unanticipated proliferation or to synthetic microbes passing their non-natural genes to natural species.[54] In a worst-case scenario, synthetic biology microbes could compete or cross-breed with natural organisms, threatening the existence or ecosystem of natural organisms.[55] Exacerbating this concern, to survive in the natural world, as opposed to a laboratory environment, synthetic biology microbes designed for bioremediation will need to be designed to be particularly robust, which could make them more competitive vis-à-vis natural organisms, as well as more difficult to control.[56] The lack of any evolutionary or ecological history, and the potential for unpredicted and unpredictable properties and interactions, will make evaluating of the consequences of a release difficult.[57]

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[53] Jonathan B. Tucker & Raymond A. Zilinskas, *The Promise and Perils of Synthetic Biology*, 12 THE NEW ATLANTIS 25 (2006), *available at* http://www.thenewatlantis.com/publications/the-promise-and-perils-of-synthetic-biology.

[54] Presidential Commission on Bioethical Issues, *supra* note 24, at 62; Andrew Balmer & Paul Martin, *Synthetic Biology: Social and Ethical Challenges*, INSTITUTE FOR SCIENCE AND SOCIETY, UNIVERSITY OF NOTTINGHAM 17 (2008), *available at* http://www.bbsrc.ac.uk/organisation/policies/reviews/scientific_areas/0806_synthetic_biology.pdf.

[55] Presidential Commission on Bioethical Issues, *supra* note 24, at 62.

[56] Dan Ferber, 303 SCIENCE 159, *Time for a Synthetic Biology Asilomar?,* Jan. 9, 2004.

[57] Presidential Commission on Bioethical Issues, *supra* note 24, at 70.

Scientists are developing potential controls, such as designing "terminator genes," making synthetic organisms dependent on non-naturally occurring nutrients, or designing organisms to self-destruct if a population spurt or density occurs.[58] But, controls are not guarantees. Living systems are complex and unpredictable, uncertainty that is only exacerbated by the unknown interaction between an organism and an ecosystem.[59] Because a synthetic biology organism could evolve or exchange genetic material with another organism, the potential controls may not be fully secure.[60] Finally, because they are living microorganisms and may be able to reproduce, synthetic biology microbes, once released, may be extremely difficult or even impossible to eliminate from the environment.[61] EPA has experience with testing and monitoring environmental releases of traditionally genetically modified microbes, including microbes developed for bioremediation, but, as discussed above, synthetic biology microbes may present additional challenges.

2. Significant New Uses

The use of synthetic biology microbes engineered for bioremediation will be subject to TSCA's significant new use requirements in certain circumstances. Similar to TSCA's new chemical substance regulations, TSCA also requires prior notification of significant new uses of chemical substances even if the substances are already listed on the TSCA Inventory.[62] Though the significant new use rules operate in a slightly different procedural manner from the new chemical substance rules, they provide the EPA with very similar substantive authority.[63] Significant new uses include uses that will change the type, form, or magnitude and duration of exposure for humans or in the environment.[64] As a result, the use of synthetic biology microbes engineered for bioremediation in various environmental situations may require successive TSCA notification as new uses. This is appropriate, as different environmental settings for the engineered microbes will present different risks and risk pathways.

3. The Endangered Species Act

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[58] *Id.* at 63; Jarred M. Callura, et. al*., Tracking, Tuning, and Terminating Microbial Physiology using Synthetic Riboregulators* (2010) *available at* http://www.pnas.org/content/107/36/15898.full; Balmer & Martin, *supra* note 54, at 17.

[59] Presidential Commission on Bioethical Issues, *supra* note 24, at 68, 137; Paras Chopra & Akhil Kamma, *Engineering Life through Synthetic Biology*, 6 IN SILICO BIOLOGY 401, 406-07 (2006).

[60] Presidential Commission on Bioethical Issues, *supra* note 24, at 68; Callura, *supra* note 58.

[61] Tucker & Zilinskas, *supra* note 53.

[62] 15 US.C. § 2604(a)(i).

[63] AM. BAR ASS'N, SECTION OF ENV'T, ENERGY, & RES., REGULATION OF NANOSCALE MATERIALS UNDER THE TOXIC SUBSTANCES CONTROL ACT 13–17 (2006), *available at* http://www.abanet.org/environ/nanotech/pdf/TSCA.pdf [hereinafter ABA, REGULATION OF NANOSCALE MATERIALS].

[64] 15 U.S.C. § 2604(a)(2). The EPA determines whether a use of a chemical substance is a significant new use based on: (A) the projected volume of manufacturing and processing of a chemical substance, (B) the extent to which a use changes the type or form of exposure of human beings or the environment to a chemical substance, (C) the extent to which a use increases the magnitude and duration of exposure of human beings or the environment to a chemical substance, and (D) the reasonably anticipated manner and methods of manufacturing, processing, distribution in commerce, and disposal of a chemical substance. *Id*.

Due to the potential for competition and interaction with natural organisms, the intentional release of synthetic biology organisms into the environment for bioremediation purposes could raise concerns under the Endangered Species Act (ESA).[65] The ESA protects listed endangered and threatened species in two general ways. First, Section 7 of the ESA prevents federal agencies from taking any action that would jeopardize a listed species.[66] Second, Section 9 of the ESA prohibits private entities from taking any action that might kill or harm a listed species, absent an acceptable mitigation plan.[67]

ESA Section 9 makes it unlawful to "take" a listed species, which is defined broadly to include killing, harming, or producing significant habitat degradation.[68] The release of synthetic biology organisms into the environment that could harm listed species, or that could result in the destruction of food sources or habitat of endangered species, could constitute a taking under the ESA and trigger both civil and criminal liability.[69] In some cases, this may require the entity desiring the release to obtain a Habitat Conservation Plan (HCP), which may allow for the incidental taking of listed species so long as the effects of the taking are minimized and mitigated, and are consistent with a number of additional requirements.[70] A synthetic biology bioremediation project that may harm certain individuals of a listed species, in an effort to better protect the species as a whole (e.g., by preventing the further spread of a hazardous release), would constitute impermissible harm under Section 9 and subject the pertinent actors to civil or criminal penalties, absent an acceptable HCP.[71]

ESA Section 7 applies to federal agency action, which includes federal agency permitting and funding of private activities.[72] Section 7 is primarily procedural, requiring federal agencies to insure through consultation that their actions do not jeopardize the continued existence of a listed species or its habitat.[73] Section 7 is based on the "best scientific and commercial data available," and does not mandate the development of new data in the face of uncertain or unknown risks.[74] The intentional release of synthetic biology organisms for bioremediation by a federal agency, or by a private party pursuant to a permit or funding from a federal agency (such as EPA), could trigger Section 7's requirements of consultation with the Fish and Wildlife Service or the National Marine Fisheries Service, the agencies responsible for implementation of the ESA.[75]

B. Chemical Production Concerns

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[65] *See generally* 16 U.S.C. §§ 1531-1540 (2006).
[66] 16 U.S.C. § 1536(a).
[67] 16 U.S.C. § 1538.
[68] 16 U.S.C. § 1532(19); *Babbitt v. Sweet Home Chapter of Communities for a Great Oregon*, 515 U.S. 687 (1995).
[69] 16 U.S.C. § 1540.
[70] 16 U.S.C. § 1539.
[71] In general, the ESA does not take into account economic criteria or any cost-benefit analysis comparing the benefit of a potential activity to its harm.
[72] 16 U.S.C. § 1536(a)(2).
[73] *Id.*
[74] *Id.*
[75] *Id.*

While manufacturers have a long history of synthetic chemical production, using synthetic biology microbes to produce chemicals creates new risks.[76] As the Presidential Commission on the Study of Bioethical Issues found, "Unlike synthetically produced chemicals, which generally have well-defined and predictable qualities, biological organisms may be more difficult to control."[77] The use of synthetic biology for chemical production raises particular concerns under the Federal Insecticide, Fungicide, and Rodenticide Act as well as some more generalized issues.

1. The Federal Insecticide, Fungicide, and Rodenticide Act

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) prohibits the distribution or sale of pesticide products in the United States without EPA registration.[78] FIFRA provides significant authority to the EPA to regulate preregistration research and development; require preregistration testing and data development; prohibit or condition the manufacture of pesticides; require submission of post-registration adverse effects information; and mandate post-registration testing requirements.[79] Unlike TSCA Section 5, FIFRA provides the EPA with sufficient authority to obtain risk data from the prospective registrant both pre- and post-registration.

Though synthetic biology microbes engineered to produce chemical pesticides may not be regulated directly under FIFRA, because the microbe itself is not a pesticide, chemical pesticides produced by such microbes would fall within FIFRA's purview.[80] A pesticide produced by a synthetic biology microbe that has the same chemical composition as an already FIFRA-registered pesticide would not require a new registration prior to use.[81] To the extent the chemical product is not fully or correctly characterized, or the synthetic biology microbe could unknowingly mutate to produce a slightly different pesticide, manufacture of such a pesticide would be in violation of FIFRA. In the absence of ongoing monitoring requirements, however, neither the EPA nor the manufacturer may know about the change until the new pesticide has already been released into the environment.

In addition to this concern, current regulations governing preregistration research and development may be inappropriate for synthetic biology microbes. EPA currently permits small scale field tests of genetically modified pesticidal organisms through a notification process.[82]

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[76] The production of chemicals using synthetic biology microbes raises a number of bioterrorism, occupational health, and other concerns, which are beyond the scope of this paper.

[77] Presidential Commission on Bioethical Issues, *supra* note 24, at 62.

[78] 7 U.S.C. § 136–136v (2000 & Supp. 2007). Pesticides regulated under FIFRA are excluded from the definition of chemical substances under TSCA. 15 U.S.C. § 2602(2)(B).

[79] 7 U.S.C. § 136a.

[80] EPA has promulgated special guidelines for genetically modified biochemical pesticides and microbial pesticides. 40 C.F.R. §§ 158.690, 158.740. These would apply where the synthetic biology microbe itself is the pesticide, as opposed to the synthetic biology microbe being used to produce a pesticide product.

[81] 7 U.S.C. § 136j(a)(1)(B). The pesticide itself would not require listing under TSCA because pesticides are exempt from TSCA; the synthetic biology microbe may be subject to TSCA, as discussed above. *See* Part I.A.. New registration under FIFRA would be required where the claims made for the registered pesticide change. 7 U.S.C. § 136j(a)(1) (C).

[82] 40 CFR 172.3(c)(1)(ii). Small scale is defined as less than ten acres of land or one acre of water, and include certain containment requirements. *Id*.

Larger field tests, up to 5000 acres, are generally governed by experimental use permits (EUPs) under FIFRA, but certain activities are exempt from the standard EUP requirements.[83] Exempt activities include tests in laboratories and greenhouses and field trials intended solely to assess a pesticide's efficacy, toxicity, or other properties.[84] These general exemptions may be inappropriate given the unique and uncertain risks of synthetic biology microbes engineered to produce pesticides.[85] In particular, due to their potential to reproduce, the field trial of a problematic synthetic biology microbe, as would be the case for any living microbe, could produce environmental contamination both by the microbe and its produced chemical product that is extremely difficult or impossible to remediate. EPA has operated a similar notification system for pest control microbes that are genetically engineered via traditional rDNA processes and has not found this problematic, though most of the registered microbes engineered through traditional genetic engineering techniques could not viably reproduce.

2. General Synthetic Biology Chemical Production Concerns

There are two primary areas of risk for synthetic biology microbes engineered for chemical production: risks stemming from the synthetic biology organism itself, and risks from the chemicals produced by the organism. These risks arise because, as discussed above, regulation of the synthetic biology microbe may fall through regulatory cracks in TSCA and FIFRA. These concerns exist both because the traditional relationship between mass and risk upon which many health and environmental statutes are based breaks down for synthetic biology microbes that can evolve and reproduce, and because the traditional method of regulating end-products may be insufficient for evaluating and adequately regulating newly manufactured microbes designed to produce the end products.

Risks from synthetic biology microbe-produced chemical products arise primarily from the potential for a synthetic biology microbe to evolve to produce a different chemical, without the manufacturer or EPA being aware of the mutation, due to a lack of ongoing monitoring or reporting requirements in most circumstances. To the extent synthetic biology chemical production evolves to produce complex chemical products, there would also be a risk that a synthetic biology produced chemical could have different properties from a traditionally produced chemical, which may not be realized due to the existing listing or registration of the traditionally produced chemical. Both of these risks can be substantially ameliorated by chemical testing, but in certain circumstances such testing would be voluntary under the existing regulatory regime.

The National Institutes of Health (NIH) does have guidelines for constructing and handling recombinant DNA organisms generally, but these guidelines apply only to research conducted by or funded by federal agencies, and do not reach private industry.[86] Although private researchers may voluntarily follow the guidelines, compliance is not required unless the research is federally

[83] 40 C.F.R. § 172.3.
[84] 40 C.F.R. § 172.3(b).
[85] Regulations permit EPA to revoke the general exemption presumptions on a case-by-case basis. 40 C.F.R. Section 172.3(e).
[86] Presidential Commission on Bioethical Issues, *supra* note 24, at 83.

funded.[87] Thus, private research concerning synthetic biology microbes engineered for chemical production may substantially take place outside of agency oversight. As discussed above, this is a particular concern because one of the much-anticipated features of synthetic biology is that it will permit a broader spectrum of small private entities and individuals to engage in the engineering of new organisms. In addition, the NIH guidelines only concern contained research and do not give any guidance concerning the deliberate release of microbes into the environment. A private researcher seeking to study microbes in the environment would not even have any best practices or guidance available concerning appropriate protective measures to take.

Conclusion

It is not surprising that a technology as potentially revolutionary as synthetic biology would raise a number of concerns under a regulatory system developed largely prior to its inception. Addressing these concerns early and proactively can permit synthetic biology to continue to develop in as rapid a manner as possible consistent with the need to adequately protect human health and the environment.

[87] DHHS, NIH Guidelines for Research Involving Recombinant DNA Molecules § 1-C-1 (2011).