

The Living Regulatory Challenges of Synthetic Biology

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ABSTRACT: The rapidly emerging technology of synthetic biology will place great strain upon the extant regulatory system due to three atypical characteristics of this nascent technology: (1) synthetic biology organisms can evolve; (2) traditional risk structures do not apply; and (3) the conventional regulatory focus on end-products may be a poor match for novel organisms that produce products. This Article presents one of the first assessments of the regulatory and oversight challenges produced by the beneficial application of synthetic biology, for energy, environmental, medical, and other purposes. Due to the uncertainty present at this early stage of synthetic biology development, and the practical political context, it is unlikely that the significant statutory and regulatory gaps identified herein could be cured directly. This Article recommends instead a selection of “soft law” alternatives that could more quickly provide flexible and adaptive measures to help fill regulatory gaps in a manner that allows this promising technology to develop as rapidly as possible, while still adequately guarding against risks to human health and the environment.

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INTRODUCTION

Synthetic biology is one of the fastest developing and most promising emerging technologies.¹ It will permit scientists to design living organisms unlike any found in nature and to redesign existing organisms to have enhanced or novel qualities.² While traditional biotechnology involves the transfer of a small amount of genetic material from one species to another, synthetic biology will permit the purposeful assembly of an entire organism. Synthetically designed organisms, it is hoped, might be put to myriad beneficial uses, including better detection and treatment of disease, the remediation of environmental pollutants, and the production of new sources of energy, medicines, and other valuable products.³ Engineered life forms, however, also might pose risks to human health and the environment. Exactly what those hazards are and how they might be controlled cannot be fully determined in advance of the very research necessary to develop this novel science in the first instance.

This Article discusses potential regulatory challenges under the existing U.S. regulatory system concerning the first synthetic biology organisms that are anticipated to be commercialized. Much of the policy and ethical commentary on synthetic biology to date has focused on biosecurity concerns associated with synthetic biology, such as the potential malevolent misuse of the technology for bioterrorism, or the possibility of accidental or intentional release of a harmful engineered organism into the community by “do it yourself” (“DIY”) synthetic biology users.⁴ While these implications of synthetic biology are of great importance, our focus here is different. We address regulatory and oversight concerns and challenges, and provide recommended strategies for dealing with the potential risks to human health and the environment from the purposeful, beneficial application of synthetic biology. Private companies, universities, and other entities are fast developing numerous legitimate uses of synthetic biology, in areas such as energy production, chemical synthesis, and bioremediation.⁵ These anticipated uses

1. Synthetic biology has been described as “arguably the world’s hottest and most poorly defined scientific discipline.” Paul Voosen, *Synthetic Biology Comes Down to Earth*, CHRON. HIGHER EDUC. (Mar. 4, 2013), <http://chronicle.com/article/Synthetic-Biology-Comes-Down/137587/>.

2. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, NEW DIRECTIONS: THE ETHICS OF SYNTHETIC BIOLOGY AND EMERGING TECHNOLOGIES 36 (2010), available at http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_o.pdf.

3. See INT’L RISK GOVERNANCE COUNCIL, POLICY BRIEF: GUIDELINES FOR THE APPROPRIATE RISK GOVERNANCE OF SYNTHETIC BIOLOGY 18–20 (2010), available at http://irgc.org/wp-content/uploads/2012/04/irgc_SB_final_07jan_web.pdf.

4. See, e.g., MICHELE S. GARFINKEL ET AL., J. CRAIG VENTER INST., SYNTHETIC GENOMICS: OPTIONS FOR GOVERNANCE 11–15 (2007), available at <http://www.synbiosafe.eu/uploads/pdf/Synthetic%20Genomics%20Options%20for%20Governance.pdf>; Laurie Garrett, *Biology’s Brave New World: The Promise and Perils of the Synbio Revolution*, 92 FOREIGN AFF. 28, 29–30 (2013).

5. Other analyses have addressed these issues from a more general and sometimes international perspective. See, e.g., INT’L RISK GOVERNANCE COUNCIL, *supra* note 3; MICHAEL

do not come without risk, risk that is sometimes referred to as “bioerror” as opposed to “bioterror.”⁶ To date, the capacity of the existing regulatory system to address these bioerror risks has received limited attention and investigation, particularly in the legal literature.

Our analysis reveals that although the extant regulatory system is capable of sufficiently handling several aspects of these novel synthetic biology organisms, there are also a number of potentially troubling 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: (1) synthetic biology organisms can evolve;⁷ (2) the traditional assumed relationship between mass and risk may break down for synthetic biology products;⁸ and (3) the conventional regulatory focus of existing statutes 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.⁹

This Article begins in Part I with an overview of synthetic biology and an examination of the potential benefits and risks of expected early synthetic biology products. The Toxic Substances Control Act (“TSCA”) is anticipated to be the most significant pre-existing regulatory authority concerning potential human health and environmental impacts of synthetic biology. Part II will examine how well TSCA is suited for this role. Part III discusses a number of other statutes, including laws pertaining to hazardous waste, endangered species, and pesticides, as well as National Institutes of Health guidelines that will also play a role in synthetic biology management.¹⁰ Part IV introduces several innovative governance approaches that could shore up some of the gaps in the existing regulatory framework for synthetic biology.

RODEMEYER, WOODROW WILSON INT’L CTR. FOR SCHOLARS, NEW LIFE, OLD BOTTLES: REGULATING FIRST-GENERATION PRODUCTS OF SYNTHETIC BIOLOGY 7 (2009), available at http://www.wilsoncenter.org/sites/default/files/nano_synbio2_electronic_final_0.pdf; Jennifer Kuzma & Todd Tanji, *Unpacking Synthetic Biology: Identification of Oversight Policy Problems and Options*, 4 REG. & GOVERNANCE 92, 93 (2010). We seek to drill down one level deeper here and evaluate the specific statutory and regulatory programs in the United States that will apply to some of these products potentially presenting environmental and health risks that will primarily fall within the regulatory jurisdiction of the U.S. Environmental Protection Agency (“EPA”).

6. Joy Y. Zhang et al., *The Transnational Governance of Synthetic Biology: Scientific Uncertainty, Cross-Borderness and the ‘Art’ of Governance* 8 (Ctr. for the Study of Bioscience, Biomedicine, Biotechnology and Society, Working Paper No. 4, 2011), available at https://royalsociety.org/~media/Royal_Society_Content/policy/publications/2011/4294977685.pdf. More technically, the risks from accidental release and exposure are often referred to as biosafety, while the risks from malevolent use are termed biosecurity.

7. See, e.g., *infra* Parts I.C.2, II.C.4.

8. See, e.g., *infra* Parts II.C.3, III.C.

9. See, e.g., *infra* Part III.A.

10. Other likely early synthetic biology products such as drugs and foods will be regulated by the Food and Drug Administration, but are beyond the scope of this paper. See Jordan Paradise & Ethan Fitzpatrick, *Synthetic Biology: Does Re-Writing Nature Require Re-Writing Regulation?*, 117 PENN ST. L. REV. 53, 55 (2012).

As with other emerging technologies, the legal and regulatory structure is incapable of evolving as rapidly as technological advance. In such cases, “soft law” approaches can provide a valuable alternative, one which can provide faster and more flexible governance that permits a promising technology to develop as rapidly as possible while adequately guarding against its potential environmental and human health risks.

I. SYNTHETIC BIOLOGY

Synthetic biology brings the concept of engineering to biology in order to design living organisms.¹¹ Although there are many different definitions of synthetic biology,¹² all recognize this emerging field as based on the understanding that DNA sequences can be assembled together like building blocks, producing a living entity with any desired combination of traits, much as one can assemble a car by putting together many individual pieces with different functions.

Synthetic biology is in its infancy as a technological field. This budding technology will use genes and other DNA sequences as interchangeable biological parts to build a target organism. The BioBricks Foundation has already developed a catalog of standardized genetic sequences that perform specified biological functions when inserted into a microorganism.¹³ Concurrently, other scientists are trying to develop a simplified genome, designed to contain the minimal genetic code necessary to survive and replicate.¹⁴ This minimal genome could then be used as a chassis to which genetic material coding for particular desired traits can be added.¹⁵ In this manner, synthetic organisms could be designed to perform myriad functions. Scientists have already achieved the first successful transfer of a synthetic genome into a bacterial cell that has had all its original genetic information removed.¹⁶

Synthetic biology represents a giant leap forward from the current generation of genetically modified organisms created by recombinant DNA.

11. Drew Endy, *Foundations for Engineering Biology*, 438 NATURE 449, 449 (2005). For a good lay description, see Andrew W. Torrance, *Synthesizing Law for Synthetic Biology*, 11 MINN. J.L. SCI. & TECH. 629, 633–38 (2010).

12. Charles W. Schmidt, *Synthetic Biology: Environmental Health Implications of a New Field*, 118 ENVTL. HEALTH PERSP. A118, A120 (2010) (“Ask 10 experts to define ‘synthetic biology,’ and you’re liable to get 10 different answers.”); Voosen, *supra* note 1 (“[A]sk five people the definition of synthetic biology, you’ll get six different answers.”).

13. Christina D. Smolke, *Building Outside of the Box: iGEM and the BioBricks Foundation*, 27 NATURE BIOTECHNOLOGY 1099, 1100 (2009); Torrance, *supra* note 11, at 656–64.

14. Brent Erickson et al., *Synthetic Biology: Regulating Industry Uses of New Biotechnologies*, 333 SCIENCE 1254, 1254 (2011); Schmidt, *supra* note 12, at A122.

15. Wil S. Hylton, *Craig Venter’s Bugs Might Save the World*, N.Y. TIMES MAG. (May 30, 2012), <http://www.nytimes.com/2012/06/03/magazine/craig-venters-bugs-might-save-the-world.html>.

16. David G. Gibson et al., *Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome*, 329 SCIENCE 52, 52 (2010).

Current genetic modification methods involve adding, modifying, or deleting one, or at most a few, genes within an organism.¹⁷ Synthetic biology, on the other hand, involves the creation of novel DNA sequences that may have never existed before in living organisms, or the widespread substitution, addition, or combination of entire or partial genomes.¹⁸ The difference between the two can be analogized to the difference between the now largely obsolete correcting typewriter that permitted small corrections in the text limited to a few characters or at most a couple lines, with the modern word processor which is capable of creating, editing, and moving large sections of text.

Synthetic biology is expected to provide significant benefits across a wide variety of fronts. Medical advances could include better disease detection, molecular devices for tissue repair and regeneration, molecules utilizing a sensor and enzymes to identify and attack disease targets such as tumors, personalized medicine, rapid development of vaccines, and cells with new properties to improve human health.¹⁹ As one example, synthetic biology may allow for less expensive production of biopharmaceuticals.²⁰ Drugs that are currently expensively produced from natural sources, such as the anticancer drug taxol and the anti-HIV compound prostratin, could be produced inexpensively through the engineering of cells to produce the compounds in large quantities.²¹

Synthetic biology is expected to produce a variety of environmental and energy benefits, including the production of chemicals in more environmentally friendly manners, bioremediation, pollutant detection, and less expensive and more efficient energy production.²² Biosensors could be designed to signal the presence of environmental contaminants, including chemical pollutants and weapons.²³ Engineered microorganisms may be able to remediate some of the most hazardous environmental pollutants, such as heavy metals, hazardous waste, and nuclear waste,²⁴ or to recycle waste such

17. See PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 36–39.

18. *Id.* at 39–50.

19. Paras Chopra & Akhil Kamma, *Engineering Life Through Synthetic Biology*, 6 IN SILICO BIOLOGY 401, 405 (2006); Warren C. Ruder et al., *Synthetic Biology Moving into the Clinic*, 333 SCIENCE 1248, 1249–51 (2011); Wilfried Weber & Martin Fussenegger, *Emerging Biomedical Applications of Synthetic Biology*, 13 NATURE REVS. GENETICS 21, 22–33 (2012).

20. European Comm'n, New & Emerging Sci. & Tech., *Synthetic Biology: Applying Engineering to Biology*, 13, EUR21796 (2005).

21. Jonathan B. Tucker & Raymond A. Zilinskas, *The Promise and Perils of Synthetic Biology*, 12 NEW ATLANTIS 25, 29 (2006).

22. Erickson et al., *supra* note 14, at 1254; European Comm'n, *supra* note 20, at 16.

23. See Arjun Bhutkar, *Synthetic Biology: Navigating the Challenges Ahead*, 8 J. BIOLAW & BUS. 19, 20 (2005); Ahmad S. Khalil & James J. Collins, *Synthetic Biology: Applications Come of Age*, 11 NATURE REVS. GENETICS 367, 368 (2010).

24. Chopra & Kamma, *supra* note 19, at 405.

as converting agricultural waste into useful products such as ethanol.²⁵ Microorganisms such as algae, bacteria, or yeast could be redesigned using synthetic biology to produce a new generation of biofuels that reduce pollution from both the production and use of the fuel.²⁶

Synthetic cells may provide a future generation of faster, less expensive, and even self-repairing computers and robotic technologies.²⁷ For example, synthetic biologists have recently figured out how to program proteins to perform basic calculations, producing the first “cellular calculator.”²⁸ Other scientists have been able to make the cellular structure of an amoeba interface with, and process sensory signals from, a robot.²⁹ Synthetic organisms may also be designed to biologically produce other proteins and chemicals with a variety of industrial, agricultural, or environmental applications,³⁰ all more efficiently, for lower cost, and using fewer natural resources than is currently possible.³¹

For all its potentially wondrous advances and benefits, synthetic biology also poses a variety of potential risks. A primary concern involves the accidental or intentional release of synthetic organisms into the environment.³² Uncontrolled release raises concerns that range from environmental damage to bioterrorism. For engineered organisms intended to be released into the environment, scientists are developing potential controls, such as making synthetic organisms dependent on non-naturally occurring nutrients or designing the organisms to self-destruct if a population spurt or density occurs.³³ Such controls instituted for synthetic organisms deliberately released into the environment to serve as biosensors, for

25. Kevin Jarrell, *Synthetic Biology: Challenges, Opportunities* (pt. 4), 6 INDUS. BIOTECHNOLOGY 325, 325 (2010); European Comm’n, *supra* note 20, at 16.

26. Chopra & Kamma, *supra* note 19, at 405; You-Kwan Oh et al., *Current Status of the Metabolic Engineering of Microorganisms for Biohydrogen Production*, 102 BIORESOURCE TECH. 8357, 8363 (2011); European Comm’n, *supra* note 20, at 16.

27. ANDREW BALMER & PAUL MARTIN, SYNTHETIC BIOLOGY: SOCIAL AND ETHICAL CHALLENGES 10 (2008), available at http://www.bbsrc.ac.uk/web/FILES/Reviews/o8o6_synthetic_biology.pdf; Soichiro Tsuda et al., *Robot Control with Biological Cells*, 87 BIOSYSTEMS 215, 222 (2007).

28. Rebecca Boyle, *Swiss Scientists Program Mammalian Cells to Work as Logic Gates*, POPULAR SCI. (June 4, 2012, 3:30 PM), <http://www.popsci.com/technology/article/2012-06/swiss-scientists-program-mammalian-cells-work-circuit-components>.

29. Tsuda et al., *supra* note 27, at 215.

30. See Erickson et al., *supra* note 14, at 1254–56; Jay D. Keasling, *Manufacturing Molecules Through Metabolic Engineering*, 330 SCIENCE 1355, 1355–58 (2010).

31. Erickson et al., *supra* note 14, at 1255; Keasling, *supra* note 30.

32. Society’s approach to synthetic biology raises other potential areas of concern beyond direct risks to human health or the environment. These could include concerns regarding global trade, justice, intellectual property rights, and other issues, as well as social, religious, and philosophical questions regarding modifying or creating life forms. These issues raise a variety of questions that have few simple answers. This Article focuses on the human health and environmental risks of synthetic biology.

33. BALMER & MARTIN, *supra* note 27, at 17.

agricultural purposes or for bioremediation, could fail, leading to environmental or human health impacts.³⁴ For example, intentionally released synthetic organisms could mutate or interact with other organisms and the environment in unexpected ways, leading to unanticipated proliferation or to synthetic organisms passing their synthetic genes to natural species.³⁵ Thus, controls are not guarantees; living systems are very complex and can be unpredictable.³⁶ Synthetic biology circuits developed so far, for instance, have tended “to mutate rapidly and become nonfunctional.”³⁷

As with other emerging technologies, the challenge of guarding against synthetic biology risks while maintaining a safe environment in which the potentially enormous benefits of synthetic biology can be pursued will fall primarily upon federal regulatory agencies. These agencies will have to seek this delicate balance while operating pursuant to a statutory and regulatory system designed largely prior to the advent of synthetic biology, or even the advent of the earlier generation of conventional, genetically modified products.³⁸ The 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 always, are designed for technologies existing at the time of the regulatory systems’ formation and are based on the then-current understanding of that technology. Such systems often face difficulty and disruption when applied to newly emerging technologies.³⁹

The first synthetic biology organisms expected to be commercialized include microorganisms engineered to produce biofuels, for chemical production, and for bioremediation.⁴⁰ The following sections provide background on each of these nascent technologies, describe how each may be used, and evaluate potential scenarios for exposure and risks to human health or the environment.

34. See Andrew Pollack, *U.S. Bioethics Commission Gives Green Light to Synthetic Biology*, N.Y. TIMES (Dec. 16, 2010), <http://www.nytimes.com/2010/12/16/science/16synthetic.html>.

35. BALMER & MARTIN, *supra* note 27, at 16–17.

36. Chopra & Kamma, *supra* note 19, at 406–07.

37. Tucker & Zilinskas, *supra* note 21, at 31.

38. See generally Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, 45 WM. & MARY L. REV. 2167 (2004) (discussing how most human health and safety and environmental laws antedate the rise of traditional biotechnology).

39. See generally INNOVATIVE GOVERNANCE MODELS FOR EMERGING TECHNOLOGIES (Gary E. Marchant et al. eds., 2013); Gregory N. Mandel, *Regulating Emerging Technologies*, 1 L. INNOVATION & TECH. 75 (2009).

40. See, e.g., PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 56 (stating “renewable energy is expected to yield the first large-scale commercial products of synthetic biology”).

A. SYNTHETIC BIOLOGY ALGAE FOR BIOFUEL PRODUCTION

Biofuels are one of the most promising new sustainable energy technologies for meeting the nation's energy needs, particularly in the transportation sector. First generation biofuels such as ethanol from corn have important limitations, including competition with food uses of the corn, loss of ecosystems, increases in food prices, and, depending on the production method, limited or even negligible environmental benefits over their life-cycle.⁴¹ Accordingly, second and third generation biofuels produced from non-food biomass are being pursued as a more sustainable, long-term solution,⁴² and single-cell algae (or microalgae) and cyanobacteria (or blue-green algae) (collectively, "algae") are leading candidates for the production of advanced biofuels.⁴³ While many researchers and companies are pursuing the development of algal cells for biofuel production using naturally occurring or genetically engineered strains, synthetic biology may offer the greatest potential for producing large quantities of sustainable biofuels by creating new strains of algae.⁴⁴ The likely use of synthetic biology algae for biofuel production presents significant opportunities, but also raises new concerns. The advantages of algae engineered using synthetic biology for energy production are summarized next, followed by a discussion of the potential risks.

1. Advantages of Synthetic Biology Algae for Biofuel Production

Genetic engineering of algae, especially synthetic biology algae, has enormous potential to improve biofuel production in algae and help make it

41. See generally Asha Parmar et al., *Cyanobacteria and Microalgae: A Positive Prospect for Biofuels*, 102 *BIORESOURCE TECH.* 10163 (2011) (examining challenges and current approaches to biofuel production).

42. See generally Miguel A. Carriquiry et al., *Second Generation Biofuels: Economics and Policies*, 39 *ENERGY POL'Y* 4222 (2011) (reviewing second generation biofuels, specifically the current cost barriers); Jasvinder Singh & Sai Gu, *Commercialization Potential of Microalgae for Biofuels Production*, 14 *RENEWABLE & SUSTAINABLE ENERGY REVS.* 2596 (2010) (recognizing microalgae feedstock as a viable biofuel).

43. See Marc Y. Menetrez, *An Overview of Algae Biofuel Production and Potential Environmental Impact*, 46 *ENVTL. SCI. & TECH.* 7073, 7074–82 (2012) (exploring algal products use in biofuels); Christie Rizk, *The Rise of the Biological Fuel*, *GENOME TECH.* (Sept. 2010), <http://www.genomeweb.com/rise-biological-fuel> ("[A]lgae is going to be the holy grail." (quoting Jerry Murphy, lead investigator at University College Cork's Sustainable Energy Research Group in Ireland) (internal quotation marks omitted)); *id.* ("[T]here is 'no question' that algae is the most promising avenue to a sustainable biofuel" (quoting Mark Hildebrand, lead investigator at University College Cork's Sustainable Energy Research Group in Ireland)).

44. Logan Christenson & Ronald Sims, *Production and Harvesting of Microalgae for Wastewater Treatment, Biofuels, and Bioproducts*, 29 *BIOTECHNOLOGY ADVANCES* 686, 698–99 (2011); Robert F. Service, *Algae's Second Try*, 333 *SCIENCE* 1238, 1238–39 (2011); Allison A. Snow & Val H. Smith, *Genetically Engineered Algae for Biofuels: A Key Role for Ecologists*, 62 *BIOSCIENCE* 765, 765 (2012).

economically competitive with other fuel types and sources.⁴⁵ There are many types of algae, but of particular importance for the production of biofuels are microalgae and cyanobacteria. These organisms are single-celled, capture sunlight through photosynthesis, and use the stored energy to convert inorganic substances into simple sugars.⁴⁶ Despite many similarities, there are some significant differences between microalgae and cyanobacteria. For example, unlike algae, cyanobacteria do not naturally produce oils, thus limiting the types of biofuels they can produce.⁴⁷ Another important difference is that algal cells must be destroyed to extract their products, while cyanobacteria secrete their products into the inter-cellular media, simplifying the extraction process.⁴⁸ Despite these differences, as the primitive ancestors of modern plants, microalgae and cyanobacteria have relatively simple cellular systems, and as a result can devote virtually all their cellular resources to the conversion of solar energy into biomass.⁴⁹ Additionally, the lack of multicellular structure allows microalgae and cyanobacteria to remain in aqueous suspension where their cellular surface area has maximum contact with nutrients such as carbon dioxide.⁵⁰

In recent years, there has been a surge of interest in utilizing algae for renewable fuel production. The policy objectives to reducing reliance on foreign energy and slowing the increase in greenhouse gas emissions have catalyzed this interest.⁵¹ For example, Exxon has given \$600 million to Synthetic Genomics, Inc. to bioengineer algae to produce “‘biocrude’⁵² . . . that can be refined into gasoline, diesel, and jet fuel.”⁵³ As a report for the Department of Energy noted, “[p]ut quite simply, microalgae are remarkable and efficient biological factories capable of taking a waste (zero-energy) form of carbon (CO₂) and converting it into a high density liquid form of energy”

45. David Biello, *The False Promise of Biofuels*, 305 SCI. AM. 58, 64 (2011); Parmar et al., *supra* note 41, at 10170–71. To be commercially successful, biofuels from algae must be equivalent or superior in performance and costs to competing liquid fuels, which include gasoline, diesel, natural gas, and biofuels (e.g., ethanol) produced from other sources of biomass such as corn, cellulosic plant material, and non-algal microbes (e.g., bacteria or yeast). *Id.*

46. JOHN SHEEHAN ET AL., NAT’L RENEWABLE ENERGY LAB., U.S. DEP’T OF ENERGY, A LOOK BACK AT THE U.S. DEPARTMENT OF ENERGY’S AQUATIC SPECIES PROGRAM: BIODIESEL FROM ALGAE 2–3 (1998), available at <http://www.nrel.gov/docs/legosti/fy98/24190.pdf>; Parmar et al., *supra* note 41, at 10164.

47. Parmar et al., *supra* note 41, at 10171.

48. Neil Savage, *The Scum Solution*, 474 NATURE S15, S16 (2011).

49. SHEEHAN ET AL., *supra* note 46, at 3.

50. *Id.*

51. See Menetrez, *supra* note 43, at 7078 (listing examples); Service, *supra* note 44, at 1238–39.

52. “Biocrude” refers to the oil-like raw product produced by a renewable energy source such as algae that, like petroleum, must then be further processed to produce a commercial fuel such as gasoline or diesel. See Colin M. Beal et al., *A Framework to Report the Production of Renewable Diesel from Algae*, 4 BIOENERGY RES. 36, 37–38 (2011).

53. Schmidt, *supra* note 12, at A121. For other examples, see Christenson & Sims, *supra* note 44, at 698–99.

(i.e., biocrude).⁵⁴ Microalgae and cyanobacteria can potentially produce a variety of biofuel feedstocks including lipids for making biodiesel and jet fuel, “hydrocarbons and isoprenoids for gasoline production and carbohydrates for ethanol production.”⁵⁵

These biofuels provide many environmental benefits—for example, “[b]iodiesel performs as well as petroleum diesel, while reducing emissions of particulate matter, CO [carbon monoxide], hydrocarbons and SO_x [sulfur oxides]. Emissions of NO_x [nitrogen oxides] are, however, higher for biodiesel in many engines.”⁵⁶ Through their photosynthetic metabolism, algal cells take in carbon dioxide and metabolize it to form high density liquid forms of energy.⁵⁷ This carbon sequestration potentially makes them attractive to renewable fuel advocates. Although the biofuel will release greenhouse gasses when burned for energy, the fuel was created by cells that sequestered carbon dioxide from the atmosphere. Consequently, making biofuel from algae is nearly carbon neutral other than the indirect carbon emissions from the energy sources used in the refining and growing processes, since the amount of carbon dioxide released when the fuel is burned is equivalent to the carbon dioxide captured from the air when the fuel is produced, producing no net increase in carbon emissions.⁵⁸

The high production capability of algae makes them an attractive source for biofuels. Algae can proliferate at a very rapid rate, doubling their mass in as little as 24 hours.⁵⁹ They can also accumulate high concentrations of oils or other feedstocks that can be used for fuel or fuel production.⁶⁰ Cyanobacteria and microalgae can convert as much as ten and five percent, respectively, of the sun’s energy into biomass, compared to one percent by traditional energy crops such as corn or sugarcane.⁶¹ Under favorable growth conditions, some algae species can produce as much as 50 to 70% of their dry weight in the form of oils.⁶² This tremendous production potential would enable algae to produce up to 58,700 liters of oil per hectare of cultivation, which is one to

54. SHEEHAN ET AL., *supra* note 46, at 3.

55. Parmar et al., *supra* note 41, at 10164; *see also* Menetrez, *supra* note 43, at 7077–78; Savage, *supra* note 48, at S15–S16.

56. SHEEHAN ET AL., *supra* note 46, at 7.

57. *Id.* at 3.

58. Anoop Singh et al., *Mechanism and Challenges in Commercialisation of Algal Biofuels*, 102 BIORESOURCE TECH. 26, 27 (2011) (“[A]lgal biofuel is . . . a carbon neutral energy source.”); Ian C. Woertz et al., *Life Cycle GHG Emissions from Microalgal Biodiesel—A CA-GREET Model*, 48 ENVTL. SCI. & TECH. 6060, 6062 (2014).

59. Yusuf Chisti, *Biodiesel from Microalgae*, 25 BIOTECHNOLOGY ADVANCES 294, 296 (2007).

60. Chun-Yen Chen et al., *Cultivation, Photobioreactor Design and Harvesting of Microalgae for Biodiesel Production: A Critical Review*, 102 BIORESOURCE TECH. 71, 71 (2011); *see also* Chisti, *supra* note 59, at 296 (noting that oil content of algae can exceed 80% of dry biomass).

61. Parmar et al., *supra* note 41, at 10163.

62. Chen et al., *supra* note 60, at 71.

two magnitudes higher than what is possible from other biofuel crops.⁶³ Algae grow to high densities and have high per-acre productivity, providing for efficient mass cultivation.⁶⁴ They are also extremely hearty organisms that thrive all over the planet and can survive in extreme conditions, such as salt water, waste water, and on land otherwise ill-suited for agriculture, which is another reason they can be more efficient for fuel production.⁶⁵

Notwithstanding the enormous hopes and expectations of microalgae biofuel production, many technological hurdles remain to widespread commercial production. One, for example, is the much needed progress in the economic scale-up of such production.⁶⁶ Moreover, existing microalgae strains need large quantities of energy, water, and nutrients for growing and processing, which makes commercial production unsustainable using existing strains.⁶⁷ Unlike high value synthetic biology products such as medicines or vaccines, the value per gallon of a fuel (regardless of how it is produced) is only a few dollars, which creates challenges in producing large quantities of such “low-end” products economically.⁶⁸ A National Academy of Sciences report in 2012 concluded that “the scale-up of algal biofuel production sufficient to meet at least 5 percent of U.S. demand for transportation fuels would place unsustainable demands on energy, water, and nutrients with current technologies and knowledge.”⁶⁹ Improvements in many algal traits are required to reduce the environmental effects per unit of fuel produced and to enhance economic viability,⁷⁰ and synthetic biology holds promise for making progress on these goals.⁷¹

Due to their simple single-cell structure, algae make easy targets for extensive genetic manipulation compared to higher plants. Scientists could engineer a number of helpful traits into algae to improve their biofuel production. Traits for producing different types of hydrocarbons could be used for improved biofuels, for secreting oils into the environment so the cells do not need to be harvested to extract their products, for better utilizing atmospheric carbon dioxide as a carbon source, and to grow faster and

63. *Id.*; see Menetrez, *supra* note 43, at 7073.

64. Parmar et al., *supra* note 41, at 10164.

65. Biello, *supra* note 45; Parmar et al., *supra* note 41, at 10164.

66. See Sophie Fon Sing et al., *Production of Biofuels from Microalgae*, 18 MITIGATION & ADAPTION STRATEGY CLIMATE CHANGE 47, 48 (2013); see also Rizk, *supra* note 43.

67. COMM. ON THE SUSTAINABLE DEV. OF ALGAL BIOFUELS, NAT'L RESEARCH COUNCIL OF THE NAT'L ACADS., SUSTAINABLE DEVELOPMENT OF ALGAL BIOFUELS IN THE UNITED STATES 2–9 (2012); Service, *supra* note 44, at 1238–39.

68. J. Craig Venter, *IB Interview: A Conversation with J. Craig Venter, PhD*, 10 INDUST. BIOTECHNOLOGY 7, 8 (2014).

69. COMM. ON THE SUSTAINABLE DEV. OF ALGAL BIOFUELS, *supra* note 67, at 2.

70. *Id.* at 6.

71. *Id.* at 42.

stronger algae in a variety of different environments, including salt water and stressed environments.⁷²

Although there are benefits, there are some limits to the maximization of algal biofuel output from the utilization of synthetic biology. Examples include the likelihood that synthetic genetics can only boost output to the point where the organism reaches its metabolic limit and that the synthetic phenotypes may not be optimal for organism survival and reproduction.⁷³ Consequently, there is the risk that synthetic phenotypes may be deselected through the process of natural selection in favor of natural traits that may be more genetically competitive.⁷⁴ However, synthetic biology may be better capable of overcoming these barriers than traditional genetic engineering techniques. Indeed, recent news stories quote American biologist Craig Venter as saying that genetic modification of natural algal strains to produce biofuels will not achieve the performance levels required to compete with existing energy sources, and that new synthetic forms of algae will be required.⁷⁵

2. Risks of Synthetic Biology Algae

The major safety and regulatory concerns about synthetic biology algae will be the environmental release, exposure, and risks of the engineered organisms.⁷⁶ A key factor influencing such concerns will be whether the algae are grown in open (i.e., open pond systems) or closed (bioreactor) systems.⁷⁷ Most commercial cultivation of algae is currently carried out in open pond systems.⁷⁸ Open cultivation utilizes uncovered “ponds” that can be either manmade or naturally occurring. By their nature, these ponds are open and exposed to the external environment. Although this open cultivation model is the easiest and least expensive way to grow algae, there are some drawbacks to this approach.⁷⁹ Open cultivation is exposed to various types of ambient changes (seasonal, weather, light, pH) that can affect growth. In addition, open systems are subject to two-way contamination, in which viruses or other pathogens can infect the pond in which the algae is grown, or cells of the

72. Biello, *supra* note 45, at 65; Savage, *supra* note 48, at S16.

73. R. Raja et al., *A Perspective on the Biotechnological Potential of Microalgae*, 34 CRITICAL REVIEWS MICROBIOLOGY 77, 85–86 (2008).

74. *Id.*

75. Ansa Varughese, *Venter's New Hope: Synthetic Algae for Biofuels*, BIOTECHNIQUES (Nov. 7, 2011), <http://www.biotechniques.com/news/Venters-New-Hope-Synthetic-Algae-for-Biofuels/biotechniques-323264.html>; *see also* Service, *supra* note 44, at 1238–39.

76. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 62–63; Snow & Smith, *supra* note 44, at 765–67.

77. Chen et al., *supra* note 60, at 72, 76.

78. *Id.* at 76.

79. Parmar et al., *supra* note 41, at 10164.

cultivated algae may escape into the environment.⁸⁰ Open pond systems also require larger areas of land than closed systems.⁸¹

The other principal but more expensive cultivation method involves photobioreactors to create a closed environment for cultivation, where conditions can be monitored and controlled. Consequently, cultivation can be maximized through a careful, controlled balancing of the variables. For example, algae grown in plastic tubes in ponds provide up to seven times the productivity of open ponds.⁸² Another comparative advantage of closed systems is the protection against unintended contamination or release of the algae.⁸³ Even with contained uses, however, the risk of accidental environmental release is not zero, although it is less than open cultivation.⁸⁴

If synthetic biology algae products are accidentally released into the environment, risks to the natural environment or human health will be very uncertain.⁸⁵ Naturally occurring algal blooms can cause large-scale fish kills and result in toxic effects in humans and animals that ingest affected waters, and it is possible that genetically engineered microalgae could cause similar or greater environmental and health risks if they escape and proliferate.⁸⁶ Modified synthetic biology algae could be transported through the air for long distances and could survive a variety of harsh environments in dormant form.⁸⁷ The risks of the release of most genetically engineered organisms into the environment create some uncertainty, and given the more substantial modifications made possible by synthetic biology, it is likely that any environmentally released synthetic biology algae will create even greater uncertainties.⁸⁸ Some of the uncertainties include: (1) the likelihood and rate of accidental release; (2) the survivability of the synthetic biology algae in the surrounding environment; (3) its ability to reproduce, spread, and compete in the natural environment; and (4) the mechanisms and magnitude of any possible risks to the environment or human health.⁸⁹

B. SYNTHETIC BIOLOGY ORGANISMS DESIGNED FOR CHEMICAL PRODUCTION

Synthetic biology may also permit scientists to engineer microorganisms into “living factories” that can produce valuable chemical products. Traditional genetic engineering is already used to produce natural chemical

80. See Sing et al., *supra* note 66, at 50.

81. Chen et al., *supra* note 60, at 76.

82. Singh & Gu, *supra* note 42, at 2597.

83. SHEEHAN ET AL., *supra* note 46, at 5.

84. Sing et al., *supra* note 66, at 52.

85. Snow & Smith, *supra* note 44, at 765–66.

86. Menetrez, *supra* note 43, at 7079–80.

87. Parmar et al., *supra* note 41, at 10,170.

88. Menetrez, *supra* note 43, at 7080–81; see also Voosen, *supra* note 1 (explaining that the risks of synthetic biology are unpredictable due to complexity and interactions of living systems).

89. Snow & Smith, *supra* note 44, at 765–66.

products through metabolic engineering. This is accomplished by transferring genetic material that produces a particular substance, such as a useful enzyme or protein, to a host microorganism that can be readily manipulated to express that substance.⁹⁰ Current biological production, however, often relies on nonrenewable resources and limited natural resources.⁹¹

1. Advantages of Synthetic Biology for Chemical Production

Synthetic biology will permit the design of microorganisms that produce chemicals metabolically with greater precision and efficiency than currently possible, and also will allow the engineering of microorganisms to produce chemicals that cannot currently be manufactured biologically.⁹² These designed microorganisms can be tailor-made for particular chemical production processes that rely on widely available and inexpensive starting materials (primarily certain sugars) to produce a broader array of valuable output chemical products.⁹³ The great advantage of the biological production of chemicals is that it can be accomplished at lower cost, using fewer natural resources, and with lower environmental impact than certain traditional chemical production methods.⁹⁴

Scientists are expected to be able to design microorganisms to produce basic commodity chemicals such as solvents, feed additives, agricultural chemicals, and certain polymers.⁹⁵ More advanced chemical products, including enzymes, vitamins, antibiotics, and nutraceuticals, may also be manufactured.⁹⁶ DuPont has developed a semi-synthetic bacteria that lives on cornstarch and produces a chemical useful for manufacturing high-tech fabrics.⁹⁷ This synthetic bacterium may become the first \$1 billion non-pharmaceutical biotechnology product.⁹⁸ Other developments include a synthetic antibiotic, a building block for Spandex, and work on a synthetic biology microorganism that would produce rubber.⁹⁹

Pharmaceutical ingredients that are too complex to be chemically synthesized may also be produced.¹⁰⁰ For example, a number of alkaloids,

90. Keasling, *supra* note 30, at 1355.

91. *Id.*

92. *Id.*

93. *Id.* at 1355-58; Erickson et al., *supra* note 14, at 1255.

94. Anastasia Krivoruchko et al., *Opportunities for Yeast Metabolic Engineering: Lessons from Synthetic Biology*, 6 BIOTECHNOLOGY J. 262, 262 (2011).

95. Keasling, *supra* note 30, at 1355-56.

96. Erickson et al., *supra* note 14, at 1255; Keasling, *supra* note 30, at 1355-56.

97. Rick Weiss, *Synthetic DNA on the Brink of Yielding New Life Forms*, WASH. POST (Dec. 17, 2007), <http://www.washingtonpost.com/wp-dyn/content/article/2007/12/16/AR2007121601900.html>.

98. *Id.*

99. Erickson et al., *supra* note 14, at 1255-56.

100. Keasling, *supra* note 30, at 1355.

compounds that are found in or derived from plants and commonly used in drugs, are likely targets for synthetic biology production.¹⁰¹ Synthetic biology may be used to more efficiently produce a precursor to artemisinin, a naturally occurring drug that is highly effective in treating malaria, but is in short supply.¹⁰² The Bill and Melinda Gates Foundation donated over \$40 million to promote research concerning the development of synthetic artemisinin.¹⁰³ Taxol, a widely used anticancer compound, and hydrocortisone are other examples of pharmaceuticals that may be produced less expensively and more efficiently through synthetic biology than current methods.¹⁰⁴

2. Risks of Synthetic Biology in Chemical Production

While manufacturers have a long history of synthetic chemical production, using synthetic biology microbes to produce chemicals biologically creates new risks. As the Presidential Commission on the Study of Bioethical Issues found, “[u]nlike synthetically produced chemicals, which generally have well-defined and predictable qualities, biological organisms may be more difficult to control.”¹⁰⁵ Although much synthetic biology chemical production is expected to take place in contained environments, this does not eliminate potential risks from unintentional release into the environment.

Further, the development of synthetic biology for chemical production also creates a risk that individuals with malicious intent could try to use toxic or pathogenic synthetic biology microorganisms for illegal activities, such as bioterrorism.¹⁰⁶ The U.S. government has developed certain recommendations to try to reduce these risks, but the synthetic biology field is in an early stage of development and understanding the contours of potential risks necessarily remains at a developmental stage as well.¹⁰⁷

C. SYNTHETIC BIOLOGY MICROORGANISMS DESIGNED FOR BIOREMEDIATION

In addition to producing biofuels and chemicals, one of the most promising uses of synthetic biology involves the potential to revolutionize the remediation of hazardous substances.¹⁰⁸ Bioremediation refers to the use of microorganisms to reduce or remove contaminants from the environment.

101. *Id.*

102. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 65; Michael Specter, *A Life of Its Own*, NEW YORKER (Sept. 28, 2009), <http://newyorker.com/magazine/2009/09/28/a-life-of-its-own>.

103. Richard Van Noorden, *Demand for Malaria Drug Soars*, 466 NATURE 672, 672 (2010).

104. Krivoruchko et al., *supra* note 94, at 271–72.

105. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 62.

106. Erickson et al., *supra* note 14, at 1256.

107. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 36. For recommendations, see *id.* at 112–66.

108. Schmidt, *supra* note 12, at A121.

Bioremediation is already common in oil spills, as several species of bacteria naturally consume and degrade certain petroleum components into less toxic byproducts.¹⁰⁹ To date, however, traditional genetic engineering of bacteria for bioremediation has been a bit of a disappointment. There have been significant difficulties with how the bacteria interact in the environment, the ability of the bacteria to compete and survive in the wild, and the low bioavailability of certain compounds.¹¹⁰ In most cases, genetically modified bacteria have not done any better at bioremediation than their naturally occurring counterparts.¹¹¹ Synthetic biology may provide a more promising alternative, the advantages and risks of which are discussed in more detail below.

1. Advantages of Synthetic Biology Bioremediation

Synthetic biology may permit the redesign of microbes to better remediate petroleum-based contamination and the engineering of novel microorganisms that can break down “more recalcitrant chemicals such as dioxins, pesticides, [and] radioactive compounds.”¹¹² Because synthetic biology microorganisms could be designed from scratch, as opposed to being dependent on naturally-occurring genetic material, they could be engineered to be more viable in the natural environment and to target particular pollutants of concern.¹¹³ These microorganisms may be able to more efficiently remediate a variety of environmental contaminants while having less of a negative impact on the environment than traditional remediation methods.¹¹⁴

2. Synthetic Biology Bioremediation Risks

Synthetic biology microbes engineered for bioremediation raise particular concerns because their use necessarily entails the intentional release of synthetic organisms into the environment.¹¹⁵ Although most synthetic biology microbes released into the environment would likely not be able to outcompete natural strains,¹¹⁶ some such microbes could mutate or

109. *Id.* at A121–22.

110. See Mareike Viebahn et al., *Effect of Genetically Modified Bacteria on Ecosystems and Their Potential Benefits for Bioremediation and Biocontrol of Plant Diseases—A Review*, in CLIMATE CHANGE, INTERCROPPING, PEST CONTROL AND BENEFICIAL MICROORGANISMS 45, 59 (Eric Lichtfouse ed., 2009); see also Ildefonso Cases & Víctor de Lorenzo, *Genetically Modified Organisms for the Environment: Stories of Success and Failure and What We Have Learned from Them*, 8 INT’L MICROBIOLOGY 213, 214 (2005).

111. Cases & de Lorenzo, *supra* note 110, at 214.

112. Schmidt, *supra* note 12, at A122; see also Viebahn et al., *supra* note 110, at 58–60.

113. Schmidt, *supra* note 12, at A120–22; Viebahn et al., *supra* note 110, at 58–60.

114. Schmidt, *supra* note 12, at A122.

115. See Genya V. Dana et al., *Four Steps to Avoid a Synthetic-Biology Disaster*, 483 NATURE 29, 29 (2012).

116. Dina Fine Maron, *The Race to Make Fuel Out of Algae Poses Risks as Well as Benefits*, N.Y. TIMES (July 22, 2010), <http://www.nytimes.com/cwire/2010/07/22/22climatewire-the-race-to>

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.¹¹⁷ In a worst-case scenario, synthetic biology microbes could compete or crossbreed with natural organisms, threatening the existence or ecosystem of those natural organisms.¹¹⁸ Exacerbating this concern, synthetic biology microbes designed for bioremediation will need to be designed to be more robust in order to survive in the natural world as opposed to a laboratory environment.¹¹⁹ This may make them more competitive in relation to naturally occurring organisms and more difficult to control. The lack of any evolutionary or ecological history, and the potential for unpredicted and unpredictable properties and interactions, will make evaluating the consequences of a release difficult.¹²⁰

Scientists are developing potential controls, such as designing “terminator genes” or “kill switches” making synthetic organisms dependent on non-naturally occurring nutrients, or designing organisms to self-destruct if a triggering stimulus or population spurt or density occurs.¹²¹ But, controls are not guarantees. Living systems are complex and unpredictable. Unknown interactions between an organism and its ecosystem only exacerbate this uncertainty.¹²² Because a synthetic biology organism could evolve or exchange genetic material with another organism, the potential controls may not be fully secure.¹²³ 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.¹²⁴ The U.S. Environmental Protection Agency (“EPA”) has experience with testing and monitoring environmental releases of traditionally genetically modified microbes, including microbes developed for bioremediation, but, as

make-fuel-out-of-algae-poses-ris-80037.html (“Changes biologists are making to the algae are designed to make them ‘big and fat and happy,’ to optimize their oil output When you do that, ‘they generally don’t survive out in the world.” (quoting Stephen Mayfield, Director of San Diego Center for Algae Biotechnology)).

117. See, e.g., BALMER & MARTIN, *supra* note 27, at 17; PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 62; Snow & Smith, *supra* note 44, at 766.

118. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 62.

119. Dan Ferber, *Microbes Made to Order*, 303 SCIENCE 158, 159 (2004).

120. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 70.

121. *Id.* at 63; see also BALMER & MARTIN, *supra* note 27, at 17; Jarred M. Callura et al., *Tracking, Tuning, and Terminating Microbial Physiology Using Synthetic Riboregulators*, 107 PROC. NAT’L ACAD. SCI. U.S.A. 15,898, 15,898 (2010); Oliver Wright et al., *Building-In Biosafety for Synthetic Biology*, 159 MICROBIOLOGY 1221, 1229 (2013).

122. See PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 68, 137; Chopra & Kamma, *supra* note 19, at 406–07.

123. See PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 68; Callura, *supra* note 121, at 15,898.

124. Tucker & Zilinskas, *supra* note 21, at 31 (“[B]ecause engineered microorganisms are self-replicating and capable of evolution, they belong in a different risk category than toxic chemicals or radioactive materials.”).

discussed above, synthetic biology microbes may present additional challenges.

II. REGULATING SYNTHETIC BIOLOGY

Synthetic biology thus presents many wondrous advances, but this potential does not come without attendant risks, risks that must be managed in some manner. As with other technologies, synthetic biology is not regulated as a technology per se. Rather, pursuant to the 1986 Coordinated Framework for Regulation of Biotechnology, synthetic biology, like earlier generations of biotechnology products before it, will be regulated based on particular product categories and particular uses.¹²⁵ As such, any synthetic biology microbes will be regulated pursuant to existing environmental and human health protection statutes.

The primary responsibility for governing the risks of synthetic biology products will fall to the EPA under the TSCA. In addition, depending on the particular products and uses, synthetic biology organisms may also be regulated pursuant to the Federal Insecticide, Fungicide, and Rodenticide Act; the Resource Conservation and Recovery Act; the Comprehensive Environmental Response, Compensation, and Liability Act; and the Endangered Species Act. The next section critically analyzes the regulatory framework governing synthetic biology products under TSCA, followed by a section which provides an equivalent analysis for the other environmental and human health statutes pertinent to synthetic biology.

A. THE TOXIC SUBSTANCES CONTROL ACT

The TSCA regulates the production, use, and disposal of hazardous chemical substances.¹²⁶ TSCA was intended as a “gap filling” statute to fill in the regulatory interstices that are not covered by other statutes.¹²⁷ Thus, 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, during, and after their use.¹²⁸ For these reasons, TSCA is likely the most important statute concerning the regulation of synthetic biology microbes engineered for biofuel production, chemical production, and bioremediation. Under the Coordinated Framework for Regulation of Biotechnology, the EPA has

125. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,302–03 (June 26, 1986). The Coordinated Framework attempts to develop a comprehensive federal regulatory policy for managing the safety of biotechnology research and products. *Id.*

126. 15 U.S.C. §§ 2601–95d (2012).

127. U.S. ENVTL. PROT. AGENCY, REGULATION OF GENETICALLY ENGINEERED SUBSTANCES UNDER TSCA 16 (1983), available at <http://www.epa.gov/nscep/index.html> (search by title and date; first result).

128. See 15 U.S.C. §§ 2601–92.

primary responsibility for regulating most genetically engineered microbes under TSCA.¹²⁹

The most important provision of TSCA for purposes of the oversight of synthetic biology products is section 5, which requires manufacturers of new chemical substances or significant new uses of existing chemicals to submit a “premanufacturing notice” (“PMN”) to the EPA before commercial production.¹³⁰ Dating back to the Coordinated Framework in 1986, the EPA has treated genetically engineered microorganisms slightly differently from other new chemical substances under TSCA. Unless otherwise exempted by EPA regulations, manufacturers of new intergeneric¹³¹ engineered microorganisms must submit a Microbial Commercial Activity Notice (“MCAN”) to the EPA for review at least 90 days prior to the commercialization of the product.¹³² The MCAN thus functions as a PMN for intergeneric genetically engineered microorganisms, but not for nonintergeneric microorganisms, based on the assumption that only the former are likely to present novel risks.¹³³

Also distinct for genetically modified microorganisms and for pre-commercialization field trials of genetically engineered microbes, the manufacturer must submit a TSCA Experimental Release Application (“TERA”) to the EPA at least 60 days prior to commencing field testing.¹³⁴ While these pre-market notification requirements of TSCA have been the primary focus of the EPA’s oversight of genetically engineered microbial products to date, various other provisions of TSCA could also apply to genetically engineered microbes in appropriate circumstances and are discussed below.

B. THRESHOLD CONCERNS: ARE SYNTHETIC BIOLOGY ORGANISMS WITHIN TSCA’S PURVIEW?

There are two threshold regulatory authority issues concerning the regulation of synthetic biology organisms pursuant to TSCA: (1) Whether living microorganisms are subject to TSCA in the first instance; and (2) whether the definition of intergeneric engineered microorganisms under TSCA might restrict the EPA’s regulatory authority with respect to synthetic biology organisms.

129. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. at 23,313.

130. 15 U.S.C. § 2604; 40 C.F.R. §§ 720.1–.122 (2013).

131. See *infra* notes 144 and 149 and accompanying text for definition of “intergeneric.”

132. 40 C.F.R. §§ 725.100–.190. This notice requirement functions as the equivalent of a PMN for traditional chemical substances under section 5 of TSCA. The EPA regulations for the MCAN and TERA contain a number of full or partial exemptions which are unlikely to apply to synthetic biology-produced microbes, and thus are not discussed here.

133. See Part II.B.2.

134. See 40 C.F.R. § 725.50.

1. Are Synthetic Biology Organisms “Chemical Substances”?

TSCA was enacted to regulate the release of “chemical substances” into the environment.¹³⁵ “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.”¹³⁶ When Congress enacted TSCA in 1976, it gave no indication that it anticipated the inclusion of living microorganisms within the definition of “chemical substance.”¹³⁷ The EPA has concluded that Congress intended “chemical substance” to be defined broadly to encompass living microorganisms¹³⁸ and consequently has relied on TSCA to regulate biotechnology products for over 25 years. To the extent that synthetic biology creates new regulatory controversies under TSCA, it could conceivably lead to a challenge to the EPA’s interpretation that living microorganisms are “chemical substances” under TSCA.

Some commentators question TSCA’s authority to reach living microorganisms.¹³⁹ The strongest argument against the EPA’s interpretation is that living microorganisms do not generally have a “particular molecular identity” pursuant to the definition of chemical substance.¹⁴⁰ The EPA contends that Congress defined the term “chemical substance” broadly and non-inclusively, and furthermore that a cell could be described as a combination of chemicals occurring in whole or in part as a result of a chemical reaction or “occurring in nature.”¹⁴¹ It is likely that the EPA’s definition would prevail in a legal challenge under the *Chevron* doctrine, which requires reviewing courts to defer to an agency’s “reasonable”

135. 15 U.S.C. § 2601.

136. *Id.* § 2602(2)(A).

137. Robin A. Chadwick, Note, *Regulating Genetically Engineered Microorganisms Under the Toxic Substances Control Act*, 24 HOFSTRA L. REV. 223, 234–35 (1995).

138. Microbial Products of Biotechnology: Final Regulation Under the Toxic Substances Control Act, 62 Fed. Reg. 17,910, 17,913 (Apr. 11, 1997) (codified at 40 C.F.R. pts. 700, 720–21, 723, 725) [hereinafter EPA, 1997a]; U.S. ENVTL. PROT. AGENCY, MICROBIAL PRODUCTS OF BIOTECHNOLOGY: FINAL REGULATION UNDER THE TOXIC SUBSTANCES CONTROL ACT—A SUMMARY OF THE PUBLIC’S COMMENTS AND THE AGENCY’S RESPONSE 7–12 (1997) [hereinafter EPA, 1997b], available at http://epa.gov/biotech_rule/pubs///pdf/coo6.pdf.

139. William G. Schiffbauer, *Regulating Genetically Engineered Microbial Products Under the Toxic Substances Control Act*, 15 ENVTL. L. REP. 10,279, 10,281–84 (1985); C. Robert Manor, Note, *Living Organisms as Chemical Substances: The EPA’s Biotechnology Policy Under the Toxic Substances Control Act*, 13 RUTGERS COMPUTER & TECH. L.J. 409, 421–23 (1987); Louis S. Sorell, Note, *Biotechnology Regulation Under the Toxic Substances Control Act*, 3 PACE ENVTL. L. REV. 57, 63–65 (1985).

140. Schiffbauer, *supra* note 139, at 10,281; Sorell, *supra* note 139, at 65.

141. U.S. ENVTL. PROT. AGENCY, *supra* note 127, at 16–17. In addition, the EPA points to the “gap-filler” objective of TSCA and the precedent of including other biological materials including bacteria, fungi, and other microorganisms on the TSCA inventory. *Id.*; see also EPA, 1997b, *supra* note 138, at 7–12 (defending application of TSCA to microorganisms).

interpretation of an ambiguous statutory provision.¹⁴² However, if challenged, there is a possibility that a court could invalidate the EPA's approach, leaving the EPA without any statutory authority to regulate modified microorganisms. Moreover, the mere possibility of such a challenge and adverse outcome may deter the EPA, at least at the margin, from regulating as aggressively as it otherwise might consider appropriate.

2. Does the EPA's Definition of "Intergeneric" Limit Synthetic Biology Regulation?

As described above, the EPA regulations under TSCA require manufacturers of new intergeneric engineered microorganisms to submit an MCAN to the EPA prior to commercialization of the product.¹⁴³ Intergeneric microorganisms are defined as organisms "formed by the deliberate combination of genetic material . . . from organisms of different taxonomic genera."¹⁴⁴ The EPA's policy is based on traditional genetic modification techniques and the premise that the transfer of genetic information from more distantly related organisms (i.e., organisms from different genera) are more likely to create new or modified traits that could present a risk.¹⁴⁵ Specifically, the EPA found that intergeneric microorganisms should be singled out for regulatory scrutiny "because of the degree of human intervention involved, the significant likelihood of creating new combinations of traits, and the greater uncertainty regarding the effects of such microorganisms on human health and the environment."¹⁴⁶

Synthetic biology, as opposed to traditional genetic modification, raises the possibility of introducing wholly synthetic genes or gene fragments (i.e., DNA sequences that do not exist in nature) into an organism.¹⁴⁷ 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.¹⁴⁸ In either case, such organisms may not be "intergeneric" under the EPA's regulatory definition because they would not include genetic material from organisms of different genera.¹⁴⁹ While the existing regulatory

142. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 845 (1984); see Schiffbauer, *supra* note 139, at 10,284 (explaining that the EPA can likely regulate genetically engineering microbes given Congressional silence on issue).

143. This notice requirement functions as the equivalent of a PMN for traditional chemical substances under section 5 of TSCA.

144. 40 C.F.R. § 725.3(2)(v) (2013).

145. EPA, 1997a, *supra* note 138, at 17,913-14; EPA, 1997b, *supra* note 138, at 19-20.

146. EPA, 1997b, *supra* note 138, at 19; see also EPA, 1997a, *supra* note 138, at 17,913.

147. See *supra* Part I.

148. As one study noted, "if individual genetic components or whole genomes are able to be designed using a computer and then chemically synthesised, concepts of 'recipient' and 'donor' organisms may lose their significance." Zhang et al., *supra* note 6, at 8.

149. With the advent of synthetic biology, the EPA's distinction between intergeneric and non-intergeneric microorganisms actually runs afoul of the Coordinated Framework's dictates

language using “intergeneric” as the differentiating principle would appear to exclude many synthetic microorganisms from regulatory review, the EPA’s stated rationale for focusing on intergeneric microorganisms—degree of human intervention, potential for new combinations, and greater uncertainty—should apply even more strongly to synthetic biology microorganisms.

The EPA, to its credit, at least partially anticipated the advent of synthetic biology and addressed this situation in the preamble to the 1986 Coordinated Framework:

In the case of chemically synthesized genes, the Agency will follow a similar principle. The genetic sequence of the synthesized gene may be identical to a sequence known to occur in an organism in the same genus as the recipient microorganism. If so, the resulting microorganism will be considered intragenetic. . . . Conversely, the sequence of the synthesized gene may be different or not known to be identical to a sequence in the genus of the recipient microorganism. In this case, the resulting product will be considered inter-generic.¹⁵⁰

However, this language was in the preamble and is not consistent with the regulatory language, which only requires a MCAN for an “intergeneric” microorganism, which is defined in the regulation as “a microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera.”¹⁵¹

Because the MCAN regulations state that they “establish[] all reporting requirements [for] microorganisms,”¹⁵² non-intergeneric genetically modified microorganisms currently are not covered by any TSCA premanufacture notice requirements. Synthetic biology modifications, however, may have a greater probability of creating a novel risk than most intragenetic transfers exempt from regulation.¹⁵³ Synthetic biology microorganisms thus create potential gaps in the current regulatory structure that do not exist for traditional genetically modified organisms.

that the products of biotechnology should be regulated based on the product itself, not based on the process by which it was made. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,315 (June 26, 1986). The EPA’s current MCAN regulations would differentiate between an intergeneric microorganism produced by traditional genetic modification techniques (which would be subject to MCAN regulations) and a synthetically-produced identical microorganism (potentially not subject to MCAN regulations).

150. *Id.* at 23,333.

151. 40 C.F.R. § 725.3(2)(v) (2013); *see supra* note 144 and accompanying text.

152. 40 C.F.R. § 725.1(a).

153. *But see* A. Wendy Russell & Robert Sparrow, *The Case for Regulating Intragenetic GMOs*, 21 J. AGRIC. & ENVTL. ETHICS 153, 175–76 (2008) (arguing that intragenetic organisms are not necessarily less risky than intergeneric organisms).

C. LIFE-CYCLE ANALYSIS OF SYNTHETIC BIOLOGY MICROBES UNDER TSCA

Like any product, synthetic biology microbes have the potential to create environmental or health risks across various stages of their life-cycle. Although no specific risks for synthetic biology microbes have been identified to date, if such risks emerge, the EPA will need to use its existing TSCA authority to address those risks. This section evaluates the potential application of, and possible challenges in applying, the pertinent regulatory provisions of TSCA to each stage of the synthetic biology microbe life-cycle.

1. Research and Development

At the research and development stage, the manufacturer of a synthetic biology microbe strain generally must submit a TSCA Experimental Release Application to the EPA at least 60 days prior to any field testing of a new strain.¹⁵⁴ The EPA then has 60 days to review the submission.¹⁵⁵ A key challenge for this field testing requirement for all genetically engineered microbes, including synthetic biology ones, is that any risks that escape the EPA's notice at the field testing stage could result in a permanent and even growing problem given the capability of living microorganisms to reproduce and proliferate. Thus, the consequences of any problem at the field testing stage could be much larger for microbes than for the traditional chemical substances for which TSCA was designed, where a problem at this stage would generally be limited to the usually small quantity of chemical used in a field test.

Imposing significant regulatory costs and burdens at the early stage of research and development, however, could have adverse impacts on innovation as many products never leave this stage and never become commercialized. The EPA must strike a delicate (and inevitably not always optimal) balance between precaution and innovation in implementing the TERA review for synthetic biology microorganisms. The increased uncertainties about the risks from synthetic biology relative to "traditional" genetically modified microbes will exacerbate this tension.

A related challenge in the research and development stage is how thoroughly and effectively the EPA can identify and address any risks created by the field testing of synthetic biology microbe products in the 60-day window provided to the agency under the TERA process. Unlike other products, such as traditional chemicals, which can be quickly evaluated by existing models,¹⁵⁶ there are no such screening methods for synthetic biology

^{154.} 40 C.F.R. § 725.250(a); *see also id.* §§ 725.250–.288 (providing the procedural requirements for the TERA, in addition to stating what it must include).

^{155.} *Id.* § 725.270(a).

^{156.} The EPA screens new chemicals based on structure activity relationships, which informs the agency of potential risks of a new chemical based on an extensive experiential database on the relationship between various molecular chemical structures and toxicity. U.S. GOV'T

products. As the EPA recognized in 1983, even before the Coordinated Framework had been published, “[s]tructure activity analyses, which form the backbone of the PMN review, will not be sufficient for analyzing risks of living organisms. Therefore, [the EPA] would have to treat each substance on a case-by-case basis.”¹⁵⁷ Given the variety and complexity of genetic manipulations made possible by synthetic biology, combined with the lack of a methodology or even track record on which to base its determinations, the EPA’s capability to reliably assess risks of field testing synthetic biology microbes in the 60 days provided by the TERA process is questionable.¹⁵⁸

Moreover, there are two exceptions to TSCA’s research and development stage requirements that raise issues for synthetic biology microorganisms. First, chemical substances used in research and development that are not manufactured “for commercial purposes” are exempt from TSCA’s premanufacture notice requirements.¹⁵⁹ “Commercial purpose” is defined broadly by the EPA under TSCA to include any production of chemical substances “with the purpose of obtaining an immediate or eventual commercial advantage.”¹⁶⁰ Private, non-“commercial purpose” activities, however, are beyond TSCA’s scope.¹⁶¹ This is a particular concern for synthetic biology because many expect synthetic biology to popularize and decentralize the development of new organisms, leading to greater non-commercial activity.¹⁶² Traditional genetic engineering requires substantial expertise, expensive laboratory equipment, and funding. Synthetic biology is likely to be available to anyone with a spare room and a few hundred dollars, spawning the so-called “DIY Bio” movement, which is expected to involve much non-commercial experimentation.¹⁶³ The inability to reach non-commercial activities thus presents a significant gap in the regulation of synthetic biology microbes.

The EPA’s definition of “commercial purpose” thus 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

ACCOUNTABILITY OFFICE, GAO-05-458, CHEMICAL REGULATION: OPTIONS EXIST TO IMPROVE EPA’S ABILITY TO ASSESS HEALTH RISKS AND MANAGE ITS CHEMICAL REVIEW PROGRAM 11 (2005).

157. U.S. ENVTL. PROT. AGENCY, *supra* note 127, at 28.

158. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 93–94.

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

160. *Id.* § 720.3(r).

161. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 94; RODEMEYER, *supra* note 5, at 36.

162. See NAT’L SCI. ADVISORY BD. FOR BIOSECURITY, ADDRESSING BIOSECURITY CONCERNS RELATED TO SYNTHETIC BIOLOGY iii (2010).

163. See Jeremy Hsu, *The Wild World of DIY Synthetic Biology*, POPULAR SCI. (Feb. 12, 2010, 3:55 PM), <http://www.popsci.com/technology/article/2010-02/future-biology-lies-designer-organisms>.

annual synthetic biology competition that involves thousands of undergraduate students building biological systems out of a set of biological parts.¹⁶⁴ 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.¹⁶⁵ 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.

Second, the TERA requirements include an exception for certain enclosed uses.¹⁶⁶ As discussed above, synthetic biology algae may be grown in open or enclosed systems. Certain research and development activities concerning synthetic biology bioremediation products may take place in enclosed environments, and most research and development for synthetic biology chemical production presumably will as well. Given the increased complexity and uncertainty about risks that synthetic biology products may present, the EPA may need to reconsider whether contained field tests of synthetic biology products should be exempted from the TERA requirement. On the other hand, such an exemption may provide an incentive for product developers to turn to contained field tests, which are likely to be the safest option.

A final issue specific to synthetic biology research and development is that some synthetic biology products may include biological containment systems designed to limit the growth of the organisms outside of a controlled environment. The TERA regulations treat “inactivation controls,” which would encompass biological containment, as equivalent to contained use, but do not provide much detail on how effective such a control system must be.¹⁶⁷ It may be appropriate to revise the TERA regulations to better elaborate and encourage such additional safety measures.

2. Pre-Commercial Notification

The most significant regulatory controls the EPA possesses under TSCA concerning synthetic biology microbes are the pre-commercialization notification requirements. TSCA section 5 authorizes the EPA to regulate new 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.¹⁶⁸ Where a chemical substance “presents an unreasonable risk,” the EPA may prohibit or limit the

164. *Id.*

165. Indeed, there is no record that iGEM participants have applied for TERA approvals.

166. 40 C.F.R. § 725.234 (2013).

167. *Id.* §§ 725-3, .234(d).

168. 15 U.S.C. § 2605(a) (2012).

amount of its manufacture or use.¹⁶⁹ Even this authority, however, is limited and could be problematic if synthetic biology microbes present significant risks.

As noted above, the developer of a new synthetic biology microbe involving the intergeneric transfer of genetic material must submit a Microbial Commercial Activity Notice to the EPA at least 90 days prior to commercialization.¹⁷⁰ The EPA then has 90 days to make a determination on whether the product will present an unreasonable risk to human health or the environment.¹⁷¹ Like the traditional premanufacture notice requirement for conventional chemicals from which it is derived through TSCA section 5, the MCAN imposes no affirmative duty on the product developer to generate any safety information, but rather only requires the developer to submit known and reasonably available data.¹⁷²

There are ongoing concerns that the EPA lacks sufficient authority to provide a meaningful safety review in 90 days in the absence of mandatory data requirements, and such concerns are even greater for synthetic biology microbes.¹⁷³ Unlike traditional chemicals, which the EPA usually evaluates using existing risk assessment models,¹⁷⁴ the EPA lacks any existing methodology or data set against which to evaluate the risks of novel synthetic biology products.¹⁷⁵ Moreover, while PMN analyses for chemicals focus on human toxicity, most significant risk scenarios for synthetic biology algae and bioremediation products involve environmental releases that may result in some form of ecological harm.¹⁷⁶ Such concerns are much more difficult to study and predict than human health risks.¹⁷⁷ 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 from synthetic biology microbes, particularly within this limited time frame, will be a significant challenge. It will be especially challenging in the early stages of synthetic

169. *Id.*

170. *See supra* note 132 and accompanying text.

171. 40 C.F.R. § 725.170.

172. In contrast, the European Union's analogous chemical regulation law, the Regulation on the Registration, Evaluation, and Authorization of Chemicals (REACH), places greater data production requirements on chemical manufacturers, depending in part on the quantity of chemical substance produced. Floor Fleurke & Han Somsen, *Precautionary Regulation of Chemical Risk: How REACH Confronts the Regulatory Challenges of Scale, Uncertainty, Complexity and Innovation*, 48 COMMON MKT. L. REV. 357, 362–70 (2011).

173. Schiffbauer, *supra* note 139, at 10,285–86.

174. *See* U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 156.

175. Schiffbauer, *supra* note 139, at 10,285–86.

176. *See supra* Part II.C.2.

177. *See, e.g.,* Robert M. Handler et al., *Evaluation of Environmental Impacts from Microalgae Cultivation in Open-Air Raceway Ponds: Analysis of the Prior Literature and Investigation of Wide Variance in Predicted Impacts*, 1 ALGAL RES. 83, 88 (2012) (noting that attempts to predict risks from environmental release of microalgae are “highly variable” due to numerous complexities and uncertainties in trying to predict risks).

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. Accordingly, there are serious doubts about the EPA's ability to identify and manage any risks that synthetic biology microbes may present using the existing MCAN mechanism.

Notwithstanding the limitations on the EPA's authority under section 5 of TSCA, the EPA has been innovative in leveraging that authority to engage product manufacturers in more proactive and collaborative safety measures. A good example is how the EPA has used its TSCA section 5 authority for nanomaterials, which have some similarities to synthetic biology microbes in that they present greater uncertainties about risk that are not amenable to being addressed using conventional risk modeling techniques. The EPA has nevertheless used its TSCA section 5 authority to persuade product manufacturers to enter into consent decrees in which the manufacturers agree to undertake additional safety measures, such as various worker protection measures (e.g., the use of personal protective equipment), conduct subchronic toxicity studies on the products, and impose restrictions on product use.¹⁷⁸ A similar approach could be developed for synthetic biology products that might come under the EPA's TSCA authority, but the challenge will be in developing a set of reasonable safety measures that can help assure the safety of the products without unduly burdening the product's commercialization. Again, because certain synthetic biology microbes primarily involve potential ecological rather than human health risks, this might be a more difficult undertaking than was the case for the EPA's treatment of nanomaterials.

Despite these significant limitations, the MCAN requirement is the EPA's most effective and powerful regulatory tool for ensuring the safety of synthetic biology microorganisms. It will be necessary for the EPA to bulk up this program with additional staff, resources, expertise, and research if it is to use its authority effectively to oversee the expected impending wave of innovative synthetic biology microbial products.

3. Safety Testing

Beyond the pre-commercialization requirements discussed above, the EPA's ability to require manufacturers to engage in any safety testing is very limited. Pursuant to TSCA section 4, the EPA may require that a product manufacturer conduct and report testing with respect to human health and environmental effects if a chemical substance either: (1) may present an "unreasonable risk of injury to health or the environment"; or (2) "will be produced in substantial quantities" and "may reasonably be anticipated to

178. See John C. Monica, Jr. & John C. Monica, *Examples of Recent EPA Regulation of Nanoscale Materials Under the Toxic Substances Control Act*, 6 NANOTECHNOLOGY L. & BUS. 388, 391 (2009).

enter the environment in substantial quantities” or result in “substantial human exposure.”¹⁷⁹ Such testing, however, can only be required after the EPA has sufficient data to meet its burden to show there may be a problem and the EPA makes a finding that existing available data are “insufficient” to determine or predict the health and environmental effects of the product.¹⁸⁰ In addition, the EPA must find that testing is “necessary to develop such data.”¹⁸¹

These requirements put a substantial evidentiary burden on the EPA before it can require a product manufacturer to conduct testing. Based on historical precedent, it often takes the EPA approximately ten years from start to finish to adopt and implement a test rule under TSCA section 4.¹⁸² The “unreasonable risk” standard is often the biggest obstacle for such a test rule, and this will likely also be the case for synthetic biology microbes. The EPA is rarely able to make a finding that a chemical substance for which it is seeking more safety data presents an “unreasonable risk”—if the EPA had sufficient data to make such a finding, it would not need to undertake more testing, but rather proceed with more direct regulatory action.¹⁸³

For these reasons, the EPA almost always supports section 4 testing requirements using the second trigger—that the product “will be produced in substantial quantities” and “may reasonably be anticipated to enter the environment in substantial quantities” or “result in substantial human exposure.” The substantial quantity measures, however, are set by statute and regulated based upon traditional chemical quantities and a direct relationship between mass and risk,¹⁸⁴ thresholds that are inappropriate for synthetic biology microbes. Further, the expectation is that in many cases synthetic biology microbes will be used in controlled and contained environments, unlike traditional chemical substances, and thus if substantial environmental release and human exposure occurs, the regulatory and risk

179. 15 U.S.C. § 2603(a)(1)(A)(i), (B)(i) (2012). 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.” TSCA Section 4(a)(1)(B) Final Statement of Policy; Criteria for Evaluating Substantial Production, Substantial Release, and Substantial or Significant Human Exposure, 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.*

180. 15 U.S.C. § 2603(a)(1)(A)(ii), (B)(ii).

181. *Id.* § 2603(a)(1)(A)(iii), (B)(iii).

182. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-07-825, CHEMICAL REGULATION: COMPARISON OF U.S. AND RECENTLY ENACTED EUROPEAN UNION APPROACHES TO PROTECT AGAINST THE RISKS OF TOXIC CHEMICALS 9, 20 (2007).

183. The European REACH Regulation again provides an alternate model, providing a burden-shifting mechanism in certain conditions. Fleurke & Somsen, *supra* note 172, at 379.

184. See Gregory Mandel, *Nanotechnology Governance*, 59 ALA. L. REV. 1323, 1367 (2008).

management systems will have already failed. It is likely that for many synthetic biology microbes 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.¹⁸⁵ In these cases, the EPA lacks statutory authority to require further testing concerning human health and environmental impacts of synthetic biology microbes.

4. Post-Market Surveillance and Risk Management

TSCA provides limited authority for the EPA to conduct post-market surveillance and risk management of regulated products such as synthetic biology microbes. TSCA section 8 provides a series of reporting and recordkeeping requirements, some of which could be important for oversight of synthetic biology microbes. For example, section 8(c) requires the manufacturer or distributor of a product to keep “records of significant adverse reactions to health or the environment alleged to have been caused by” their product.¹⁸⁶

EPA regulations limit such recordkeeping to “known” human health effects and a variety of environmental effects, including:

- (1) Gradual or sudden changes in the composition of animal life or plant life, including fungal or microbial organisms, in an area.
- (2) Abnormal number of deaths of organisms (e.g., fish kills).
- (3) Reduction of the reproductive success or the vigor of a species.
- (4) Reduction in agricultural productivity, whether crops or livestock.
- (5) Alterations in the behavior or distribution of a species.
- (6) Long lasting or irreversible contamination of components of the physical environment, especially in the case of ground water, and surface water and soil resources that have limited self-cleansing capability.¹⁸⁷

Several of these triggers would presumably apply to any accidental environmental release of, or adverse effects from, synthetic biology microbes, such as alterations in the distribution of a species or long-lasting contamination of the environment. However, the effectiveness of this provision is limited in two key ways. First, a company is only required to maintain records of allegations of such effects, and not to itself identify or mitigate such effects.¹⁸⁸ Second, the company is only required to retain the information and is not required to report the allegations to the EPA.¹⁸⁹

185. Schiffbauer, *supra* note 139, at 10,284–85.

186. 15 U.S.C. § 2607(c).

187. 40 C.F.R. § 717.12(c) (2013).

188. *See id.* § 717.12.

189. *See id.* § 717.15 (requiring firms to only keep records of allegations and only requiring firms to transfer those records to the EPA when the firm ceases to exist).

Section 8(e) of TSCA requires the manufacturer or distributor of a product to report to the EPA any information that “reasonably supports the conclusion that [the chemical] substance or mixture presents a substantial risk of injury to health or the environment.”¹⁹⁰ The EPA has not issued regulations implementing section 8(e) to date, so it is not clear precisely what type of scenarios relating to synthetic biology microbes would trigger reporting requirements under this provision. However, given the statutory language of “substantial risk,” as well as the historical implementation of this provision, it is likely that results showing actual or serious potential for harm would be required, and this may not encompass some of the key incidents that would be important to report to the EPA about synthetic biology microbes, such as unintended environmental releases that may not trigger section 8(e) but which nevertheless may be of concern to the EPA.

If the EPA identifies potential post-marketing risks associated with synthetic biology microbes, it potentially could take regulatory action under section 6 of TSCA to attempt to manage those risks. Section 6 of TSCA gives the EPA an extensive menu of potential risk management options including prohibition of a product, restrictions on the quantity or use of a product, requirements for labeling or communicating the risks of a product, restrictions on product disposal, testing requirements, and reporting requirements.¹⁹¹ However, to impose such a requirement, the EPA must make a finding based on a quantified cost-benefit calculation that the product poses an “unreasonable risk,”¹⁹² and moreover that the proposed regulatory action is the least burdensome for protecting against the unreasonable risk.¹⁹³ As enforced by the courts, these requirements are very difficult for the agency to satisfy.¹⁹⁴ Indeed, the EPA has issued rules under section 6 for only five chemicals since the statute was enacted in 1976 (polychlorinated biphenyls, fully halogenated chlorofluoroalkanes, dioxin, asbestos, and hexavalent chromium).¹⁹⁵ One of these, a proposed ban on certain asbestos products, was based on ten years of study and a 45,000-page record, but was struck down by a federal appeals court in 1991 for lacking sufficient cost-benefit analysis and not imposing the least burdensome regulation.¹⁹⁶ The EPA has not tried to exercise this authority subsequently. For these reasons, TSCA (or the judicial interpretation of TSCA) has been criticized by commentators for

190. 15 U.S.C. § 2607(e).

191. *Id.* § 2605(a).

192. *Id.*

193. *See id.* § 2605(c)(4)(B).

194. *Corrosion Proof Fittings v. EPA*, 947 F.2d 1201, 1220 (5th Cir. 1991).

195. U.S. GOV'T ACCOUNTABILITY OFFICE, *supra* note 156, at 27.

196. *See Corrosion Proof Fittings*, 947 F.2d at 1215–16 (striking down the EPA's final rule asbestos ban).

imposing unrealistic data and certainty requirements.¹⁹⁷ Considering the limited scientific knowledge concerning the risks of synthetic biology microbes, it would be difficult, if not impossible, for the EPA to conduct the necessary cost-benefit analysis to satisfy the least burdensome regulation requirement.

The lack of serious post-commercialization surveillance or authority represents a significant concern for synthetic biology microbes, particularly bioremediation or algae products that may be intentionally placed into the open environment. Organisms can evolve.¹⁹⁸ A synthetic biology microbe may mutate, creating both a new organism and new chemical products produced by that organism, all without the manufacturer's or the EPA's knowledge. These new organisms and chemical products could have different risk profiles than the intended products. Developers may be able to design synthetic biology microbes so that the risk of evolution is low, but biological controls can fail.¹⁹⁹ In addition, because of some of the potential regulatory gaps and exemptions discussed above, regulators may not have appropriately evaluated synthetic biology microbes' risks related to evolution and other concerns in the first instance.²⁰⁰ This represents a major gap for the regulatory oversight of synthetic biology microbes under TSCA—if a risk exists and the EPA fails to identify and address that risk in the brief MCAN window of opportunity, or if the EPA never had an opportunity to assess the risk, the agency may be without any effective regulatory authority to recognize or manage subsequent damage.

5. Disposal

The final stage of a product life-cycle is disposal, which could represent a significant risk scenario for synthetic biology microbes. If large quantities of algae are processed to produce fuels, industrial chemicals, or bioremediation products, the residual biomass must be disposed of in some manner and could consist of relatively large quantities of materials. If some living cells survive the processing step, they may exist in the waste material and potentially grow and proliferate if not properly handled.²⁰¹ TSCA section 6 does provide for risk management actions necessary to ensure the safe disposal of a material, but such requirements can only be imposed under the strict risk-benefit criteria of section 6. These requirements make it unlikely that such risk management

197. Albert C. Lin, *Size Matters: Regulating Nanotechnology*, 31 HARV. ENVTL. L. REV. 349, 362–67 (2007) (discussing critiques of TSCA).

198. James Anderson et al., *Engineering and Ethical Perspectives in Synthetic Biology*, 13 EMBO REP. 584, 587 (2012).

199. See *supra* notes 33–37 and accompanying text.

200. 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.

201. See Snow & Smith, *supra* note 44, at 766.

can ever be imposed for synthetic biology microbes (or any other product) under the existing statutory provision. Other statutes, however, also govern product disposal, a topic considered below.²⁰²

D. TSCA'S OVERALL EFFECTIVENESS AND RELEVANCE

TSCA is the most applicable and relevant statutory program for regulating any potential health and environmental risks from synthetic biology microbes. Given the limits inherent in the current statute and regulations, however, the EPA will have a very difficult role to play under TSCA, both in adequately protecting against human health and environmental risks and in balancing the need to conduct adequate risk assessments against the desire to permit this nascent technology to develop without undue regulatory burdens.

It is not clear at this stage whether and to what extent synthetic biology microbes will present significant risks. If the risks of such products are small and manageable, the existing MCAN mechanism may be sufficient to protect public health and the environment. But, to the extent synthetic biology microbes create unanticipated or significant risks, the MCAN process and other existing TSCA statutory provisions are likely deficient in anticipating and managing those risks.

Many have criticized TSCA as an ineffective and outdated regulatory framework for regulating toxic substances generally.²⁰³ There is now some consensus that the statute needs a comprehensive revision, and there have been a number of bills introduced in Congress recently, garnering widespread support, to substantially strengthen TSCA.²⁰⁴ While there are important differences in the bills introduced to date, the general direction of the revisions is to require manufacturers of chemical substances to produce a minimum set of safety data before commercializing their products.²⁰⁵ The proposed legislation will also ease the procedural and substantive burdens on the EPA to promulgate risk management rules under TSCA section 6. These revisions, if adopted, would significantly enhance the ability of TSCA to regulate synthetic biology microbes, although the precise implications for synthetic biology will depend on the final details of any legislation that Congress enacts.

202. See *infra* Part III.

203. See, e.g., David Markell, *An Overview of TSCA, Its History and Key Underlying Assumptions, and Its Place in Environmental Regulation*, 32 WASH. U. J.L. & POL'Y 333, 344–50, 369–75 (2010) (surveying many of the issues and criticisms surrounding TSCA).

204. E.g., Chemical Safety Improvement Act, S. 1009, 113th Cong. (2013) (proposing “[t]o reauthorize and modernize the Toxic Substances Control Act”).

205. LINDA-JO SCHIEROW, CONG. RESEARCH SERV., R43136, PROPOSED REFORM OF THE TOXIC SUBSTANCES CONTROL ACT (TSCA) IN THE 113TH CONGRESS: S. 1009 COMPARED WITH S. 696 AND CURRENT LAW 2–3 (2013). Presumably, such requirements would apply to synthetic biology microbes. See *supra* Part II.B.

III. SYNTHETIC BIOLOGY REGULATION BEYOND TSCA

In addition to TSCA, several additional human health and environmental statutes are pertinent to the regulation of synthetic biology microbes engineered for biofuels, chemical production, and bioremediation. These statutes include the Federal Insecticide, Fungicide, and Rodenticide Act; the Endangered Species Act; the Resource Conservation and Recovery Act; and the Comprehensive Environmental Response, Compensation, and Liability Act.²⁰⁶ In addition, the National Institutes of Health also has guidelines pertinent to the handling of synthetic biology microorganisms.²⁰⁷ As discussed in the following sections, some of these statutes and guidelines are applicable to all types of synthetic biology microbes discussed here, while others are limited to particular synthetic biology applications.

A. THE FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

The use of synthetic biology to develop microbes designed for industrial chemical production raises particular concerns under the Federal Insecticide, Fungicide, and Rodenticide Act (“FIFRA”). FIFRA prohibits the distribution or sale of pesticide products in the United States without EPA registration.²⁰⁸ 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.²⁰⁹ Unlike TSCA section 5, FIFRA provides the EPA with sufficient authority to obtain risk data from the prospective registrant both pre- and post-registration. These provisions apply only to pesticide products, likely a small subset of the products expected to be produced by synthetic biology.

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.²¹⁰ A pesticide produced by a synthetic biology microbe that has the same chemical composition as an already FIFRA-

206. See *infra* Parts III.A–D.

207. See *infra* Part III.E.

208. 7 U.S.C. § 136a(a) (2012). Pesticides regulated under FIFRA are excluded from the definition of chemical substances under TSCA. 15 U.S.C. § 2602(2)(B)(ii) (2012).

209. 7 U.S.C. § 136a(c) (2012).

210. The EPA has promulgated special guidelines for genetically modified biochemical pesticides and microbial pesticides. 40 C.F.R. § 158.690 (2007) (biochemical pesticides); *id.* § 158.740 (microbial pesticides). 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.

registered pesticide would not require a new registration prior to use.²¹¹ 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 given that the existing approval would not cover the mutated version. 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 concerns about an unknown release, current regulations governing preregistration research and development may be inappropriate for synthetic biology microbes. The EPA currently permits small-scale field tests of genetically modified pesticidal organisms through a notification process.²¹² Larger field tests, up to 5000 acres, are generally governed by experimental use permits (“EUPs”) under FIFRA.²¹³ Certain activities are exempt from the standard EUP requirements, including tests in laboratories and greenhouses and field trials intended solely to “assess [a] pesticide’s potential efficacy, toxicity, or other properties.”²¹⁴ These general exemptions may be inappropriate given the unique and uncertain risks of synthetic biology microbes engineered to produce pesticides.²¹⁵ In particular, due to their potential to reproduce, the field trial of a problematic synthetic biology microbe could produce environmental contamination both by the microbe and its produced chemical product that is extremely difficult or impossible to remediate. The 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.²¹⁶

B. THE ENDANGERED SPECIES ACT

Due to the potential for competition and interaction with natural organisms, the intentional release of synthetic biology organisms into the environment for bioremediation purposes, or synthetic biology algae raised in open environments, could raise concerns under the Endangered Species

211. See 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 II.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).

212. 40 C.F.R. §§ 172.3(c)(1), 172.43–59 (2013). “[S]mall-scale” is defined as less than ten acres of land or one acre of water and includes certain containment requirements. *Id.* § 172.3(c)(1)–(2).

213. *Id.* § 172.3(a).

214. *Id.* § 172.3(b)(1).

215. Regulations permit the EPA to revoke the general exemption presumptions on a case-by-case basis. *Id.* § 172.3(e).

216. *Id.* § 172.57.

Act (“ESA”).²¹⁷ ESA protects listed endangered and threatened species in two general ways. First, section 7 of ESA prevents federal agencies from taking any action that would jeopardize a listed species.²¹⁸ Second, section 9 of ESA prohibits private entities from taking any action that might kill or harm a listed species, absent an acceptable mitigation plan.²¹⁹

ESA section 7 applies to federal agency action, which includes federal agency decisions to grant permits and to federal agency funding of private activities.²²⁰ Section 7 is primarily procedural, requiring federal agencies to ensure through consultation that their actions do not jeopardize the continued existence of a listed species or its habitat.²²¹ Section 7 decisionmaking must be 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.²²² A federal agency’s intentional release of synthetic biology organisms for bioremediation, or a private party’s release pursuant to a permit or funding from a federal agency such as the EPA, could trigger section 7’s requirements of consultation with the agencies responsible for implementation of ESA.²²³

ESA section 9 makes it unlawful to “take” a listed species, which is defined broadly to include killing, harming, or producing significant habitat degradation.²²⁴ 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 or threatened species, could constitute a taking under ESA and trigger both civil and criminal liability.²²⁵ 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.²²⁶ A synthetic biology bioremediation project that may harm

217. See 16 U.S.C. §§ 1531–44 (2012); see *id.* § 1531(b) (stating the ESA’s purpose to conserve the environmental ecosystems that endangered species rely upon).

218. *Id.* § 1536(a).

219. *Id.* § 1538(a).

220. *Id.* § 1536(a)(2).

221. *Id.*

222. *Id.*

223. See *id.* The agencies responsible for implementing ESA are the Fish and Wildlife Service or the National Marine Fisheries Service. See *id.* § 1537a(a); 50 C.F.R. § 402.01(b) (2013). On ESA section 7 triggering consultation requirements, see, e.g., *Ctr. for Food Safety v. Johanns*, 451 F. Supp. 2d 1165, 1182–83 (D. Haw. 2006) (holding that the Department of Agriculture’s approval of field testing of genetically engineered plant producing pharmaceuticals violated the Endangered Species Act).

224. 16 U.S.C. § 1532(19); *Babbitt v. Sweet Home Chapter of Cmty. for a Great Or.*, 515 U.S. 687, 690–91 (1995).

225. 16 U.S.C. § 1540.

226. *Id.* § 1539.

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.²²⁷

C. THE RESOURCE CONSERVATION AND RECOVERY ACT

The Resource Conservation and Recovery Act (“RCRA”),²²⁸ which amended the Solid Waste Disposal Act,²²⁹ regulates the generation, transportation, management, and disposal (other than to surface water) of solid and hazardous wastes.²³⁰ RCRA also contains groundwater monitoring and corrective action requirements that apply to hazardous waste releases.²³¹ A waste is subject to RCRA’s requirements if it has been listed by the EPA or if it exhibits certain hazardous characteristics, such as those that would pose a threat to human health or the environment.²³² Synthetic biology microbes engineered to produce biofuels, chemical products, or for bioremediation that meet the definition of RCRA hazardous wastes will be subject to RCRA’s disposal and other requirements. Most such microbes, however, would not be expected to exhibit hazardous characteristics, and therefore would likely require the EPA listing to be subject to RCRA’s purview.²³³ The EPA’s listing of new hazardous wastes under RCRA is notoriously slow, so it is unlikely that synthetic biology organisms will be listed as hazardous wastes any time soon.

The 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

227. 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.

228. Resource Conservation and Recovery Act of 1976, Pub. L. No. 94-580, 90 Stat. 2795 (1976) (codified at 42 U.S.C. §§ 6901–92k (2012)).

229. 42 U.S.C. §§ 6901–92k (2012).

230. 40 C.F.R. pts. 260–79 (2013).

231. 40 C.F.R. §§ 264.92–.101. See generally OFFICE OF SOLID WASTE, U.S. ENVTL. PROT. AGENCY, RCRA GROUND-WATER MONITORING: DRAFT TECHNICAL GUIDANCE (1992), available at http://www.epa.gov/osw/hazard/correctiveaction/resources/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.

232. 42 U.S.C. § 6903(5); 40 C.F.R. § 261.3.

233. Hazardous waste designations can apply automatically to wastes that meet defined “characteristics” (e.g., toxicity, reactivity, corrosivity, ignitability) or by regulation to wastes specifically listed as hazardous by the EPA. Synthetic biology algae wastes would likely not meet any of the characteristics, so they would have to be listed to be designated as hazardous.

generator[s].”²³⁴ The EPA’s current classification scheme for RCRA waste generators may not be appropriate for synthetic biology products, however, because the toxicity of a synthetic biology microbe may not bear the same relation to mass as for traditional waste.

D. 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.²³⁵ CERCLA liability and enforcement authority generally turns on whether a release involves a “hazardous substance,” a term defined broadly under the statute.²³⁶ 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.”²³⁷ However, the EPA must list the specific organism prospectively, before the release occurs, to have any deterrent effect in preventing releases, something the EPA has not yet shown any indication of doing. To the extent a synthetic biology microbe is indeed 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.

E. NATIONAL INSTITUTES OF HEALTH GUIDELINES

The U.S. National Institutes of Health (“NIH”) could also play a role in managing synthetic biology risks, but its authority is limited in this regard. The NIH has 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.²³⁸ Although private researchers may voluntarily follow the guidelines, compliance is not required unless the research is federally funded.²³⁹ Thus, private research concerning synthetic biology microbes engineered for chemical production may substantially take place outside of agency oversight.

²³⁴. U.S. ENVTL. PROT. AGENCY, MANAGING YOUR HAZARDOUS WASTE: A GUIDE FOR SMALL BUSINESSES 3 (2001), available at <http://www.epa.gov/osw/hazard/generation/sqg/handbook/ko1005.pdf>; see also 40 C.F.R. § 261.5.

²³⁵. 42 U.S.C. §§ 9601–75.

²³⁶. *Id.* §§ 9601(14), 9607(a).

²³⁷. *Id.* § 9602(a).

²³⁸. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 83.

²³⁹. DEP’T HEALTH & HUMAN SERVS., NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES) § I-C-1 (2013).

As discussed above, governance of private research activities is of particular concern for synthetic biology 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. While traditional genetic engineering techniques require substantial monetary and laboratory resources, individuals are expected to be able to engage in synthetic biology activities in their home and with limited resources.

Finally, 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.

IV. INNOVATIVE SYNTHETIC BIOLOGY GOVERNANCE

The previous Part reveals that, as was the case with the first generations of genetically engineered products, a matrix of existing statutes and regulatory programs exist to provide regulatory oversight of synthetic biology products. However, as was also the case for the earlier generation of genetically engineered products,²⁴⁰ the existing statutory matrix has various gaps and mismatches for synthetic biology, perhaps even greater than those for the first generation of genetically engineered products. And, familiar battle lines are already being drawn. Various public interest and advocacy groups are expressing concern and mobilizing opposition to synthetic biology, calling for application of the precautionary principle to impose an immediate “moratorium on the release and commercial use” of synthetic biology.²⁴¹ On the other hand, President Obama’s Presidential Commission for the Study of Bioethical Issues has rejected applying the precautionary principle for synthetic biology (as well as its opposite “extreme” of no oversight), and instead has called for “responsible stewardship” and “prudent vigilance” of synthetic biology.²⁴²

Absent some unexpected tragedy or disaster, there is unlikely to be sufficient impetus for major statutory overhaul or change in the near future, except perhaps for the major revisions to TSCA that are pending in Congress.²⁴³ This is not surprising: major statutory or regulatory change is politically difficult, time-consuming, and expensive. Further, the uncertainties about the technological trajectory and risks of synthetic biology, the wide range of products and applications, and the promising

240. See generally Mandel, *supra* note 39.

241. FRIENDS OF THE EARTH ET AL., THE PRINCIPLES FOR THE OVERSIGHT OF SYNTHETIC BIOLOGY 3 (2012), available at http://libcloud.s3.amazonaws.com/93/ae/9/2287/2/Principles_for_the_oversight_of_synthetic_biology.pdf.

242. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 25–27.

243. See *supra* notes 204–05 and accompanying text.

environmental, health, and economic benefits of synthetic biology all counsel against major new regulatory impositions at this time.²⁴⁴ However, this necessary lack of regulation may create what the International Risk Governance Council has described as “risk governance deficits.”²⁴⁵

While new regulatory provisions may be premature, other types of innovative “soft law” measures could help to fill the current gaps until such time as the need for, and focus of, formal regulation has been better delineated.²⁴⁶ Soft law measures can produce flexible interim (or long-term) measures that can more rapidly enable a sound oversight system. In addition to allowing a promising technology to develop while protecting human health and the environment, such measures can also help to maintain public confidence, provide industry with some certainty concerning regulatory requirements, and assure investors that the technology will be developed safely and without unduly restrictive regulatory burdens.²⁴⁷

Soft law measures can include voluntary programs, consensus standards, partnership programs, codes of conducts, principles, and certification programs. They can impose substantive expectations or requirements, but unlike traditional “hard law” government regulations, soft law measures are not directly enforceable. Soft law approaches often overlap with “new governance” modes of oversight, which expand oversight from government to broaden responsibility to other stakeholders including industry actors, non-governmental organizations (“NGOs”), and other third parties and experts.²⁴⁸

As the Presidential Commission noted, the rapidly developing pace of synthetic biology requires an iterative response, in which “decisions [are] revisited and amended as warranted by additional information about risks and potential benefits.”²⁴⁹ These soft law and governance approaches have a number of potential advantages,²⁵⁰ including that they can often be adopted more rapidly and amended more quickly than traditional regulation,

244. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 26.

245. INT'L RISK GOVERNANCE COUNCIL, *supra* note 3, at 26–28.

246. See, e.g., John J. Kirton & Michael J. Trebilcock, *Introduction: Hard Choices and Soft Law in Sustainable Global Governance*, in *HARD CHOICES, SOFT LAW: VOLUNTARY STANDARDS IN GLOBAL TRADE, ENVIRONMENT AND SOCIAL GOVERNANCE* 3, 8–9 (John J. Kirton & Michael J. Trebilcock eds., 2004); Kenneth W. Abbott & Duncan Snidal, *Hard and Soft Law in International Governance*, 54 INT'L ORG. 421, 434–36, 444–50 (2000); Kenneth W. Abbott et al., *Soft Law Oversight Mechanisms for Nanotechnology*, 52 JURIMETRICS J. 279, 300–01 (2012); Diana M. Bowman & Graeme A. Hodge, 'Governing' Nanotechnology Without Government?, 35 SCI. & PUB. POL'Y 475, 479–84 (2008); Gurumurthy Ramachandran et al., *Recommendations for Oversight of Nanobiotechnology: Dynamic Oversight for Complex and Convergent Technology*, 13 J. NANOPARTICLE RES. 1345, 1348–50 tbl.1 (2011).

247. See Abbott et al., *supra* note 246, at 300–02.

248. David H. Guston & Daniel Sarewitz, *Real-Time Technology Assessment*, 24 TECH. SOC'Y 93, 107–08 (2002); see also INT'L RISK GOVERNANCE COUNCIL, *supra* note 3, at 37–39; Mandel, *supra* note 39, at 75, 90–91; O. Renn & M.C. Roco, *Nanotechnology and the Need for Risk Governance*, 8 J. NANOPARTICLE RES. 153, 157–58 (2006).

249. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 27.

250. See *supra* note 248 and accompanying text.

providing a more adaptive oversight system.²⁵¹ Unlike traditional laws, soft law measures can often be extended beyond national and regional boundaries, and are usually based on a collaborative rather than adversarial model. The Presidential Commission noted that “[s]elf-regulation also promotes a moral sense of ownership within a professional culture of responsibility.”²⁵²

Soft law approaches should not be considered a panacea—there are some potential disadvantages in addition to the advantages that soft law can provide. For example, such measures may not provide the normal procedural safeguards that are an important part of traditional regulation and may reduce transparency or exclude relevant stakeholders from the decisionmaking process. In addition, traditional regulation has important secondary benefits beyond its primary objective of protecting public health and the environment, such as by providing consumer confidence that a technology or industry is being kept in check by government regulation and providing certainty to companies and investors about regulatory requirements. There is some evidence that voluntary soft law programs are less effective than traditional regulation in providing these secondary benefits. Studies have shown that the public has less confidence in voluntary programs providing adequate oversight than those that are mandatory.²⁵³

Companies involved in some aspects of synthetic biology, such as gene synthesis companies, have already instituted some innovative self-regulatory programs to prevent misuse of synthetic DNA for bioterrorism or other malevolent uses.²⁵⁴ Similar innovative ideas using soft law approaches would be helpful to begin addressing the types of environmental risks from the synthetic biology applications discussed here, such as algae biofuels and bioremediation. Over time, these soft law approaches, which can be established relatively quickly and without a lot of red tape, can gradually be hardened into more traditional “hard law” regulatory requirements.²⁵⁵

251. Jessica Tucker et al., *Standards for Synthetic Biology*, 26 ISSUES SCI. & TECH. 5, 9 (2010); see also INT’L RISK GOVERNANCE COUNCIL, *supra* note 3, at 27 (“[A]ny effective approach to risk governance of synthetic biology must be capable of evolving as scientific and technical knowledge expands, requiring flexibility in the face of uncertainty about the eventual nature of products, processes, benefits and risks.”).

252. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 28.

253. See JANE MACOUBRIE, INFORMED PUBLIC PERCEPTIONS OF NANOTECHNOLOGY AND TRUST IN GOVERNMENT, PROJECT ON EMERGING NANOTECHNOLOGY, WOODROW WILSON INT’L CTR. FOR SCHOLARS, 3–4 (2005) (reporting that a strong majority opposed voluntary oversight of nanotechnology); Jennifer Kuzma et al., *Evaluating Oversight Systems for Emerging Technologies: A Case Study of Genetically Engineered Organisms*, 37 J.L. MED. & ETHICS 546, 565–66 (2009); Eleonore Pauwels, *Public Understanding of Synthetic Biology*, 63 BIOSCIENCE 79, 86 (2013) (reporting that 52% of the public thought government should oversee synthetic biology, while 36% believed “voluntary guidelines developed jointly by industry and government would provide adequate oversight”).

254. Yudhijit Bhattacharjee, *Gene-Synthesis Companies Join Forces to Self-Regulate*, 316 SCIENCE 1682, 1682 (2007); Zhang et al., *supra* note 6, at 19.

255. Gary E. Marchant et al., *Risk Management Principles for Nanotechnology*, 2 NANOETHICS 43, 53–54 & fig.3 (2008).

One approach would be an industry-NGO partnership similar to the NanoRisk Framework that was developed jointly by a large product manufacturer, DuPont, and a leading environmental organization, the Environmental Defense Fund.²⁵⁶ This partnership provided a publicly available framework for nanotechnology companies to undertake “a systematic and disciplined process” for evaluating and addressing the risks of their products using nanoscale materials.²⁵⁷ The participation of both an industry and NGO partner helped to ensure this framework was reasonable, effective, and credible. As an example of how such soft law programs can gradually harden into more formal requirements, the International Organization for Standardization recently incorporated the NanoRisk Framework into its nanotechnology risk management standard.²⁵⁸ In the same way, a credible and balanced risk assessment and management tool for synthetic biology jointly developed by one or more industry and NGO participants could provide a standard for synthetic biology safety assessments that eventually becomes adopted by regulatory agencies.

Another soft law approach would be to establish some type of “issue manager,” consisting of a multi-stakeholder coordinating body, that would be helpful to orchestrate the research and regulatory actions of the various governmental agencies that may have some oversight responsibilities for synthetic biology.²⁵⁹ An instructive precedent might be the National Nanotechnology Initiative (“NNI”), including its National Nanotechnology Coordination Office (“NNCO”) that provides administrative support and coordination, and the Nanoscale Science, Engineering, and Technology (“NSET”) Subcommittee composed of representatives of federal agencies with an interest in nanotechnology.²⁶⁰ The NNI with its various subcomponents serves as a focus for media, industry, and interested stakeholders to interact with the government and each other on issues relating to nanotechnology, including safety and regulatory issues. The NNI also coordinates important initiatives such as research and development planning and coordination, and even issues guidance such as a common definition of nanotechnology. A similar coordinating body for synthetic biology would likewise help to provide some coherence and central organization for the rapidly evolving and sprawling field of synthetic

256. See generally ENVTL. DEF.-DUPONT NANO P'SHIP, NANORISK FRAMEWORK (2007).

257. *Id.* at 7.

258. Abbott et al., *supra* note 246, at 290.

259. Gary E. Marchant & Wendell Wallach, *Governing the Governance of Emerging Technologies*, in INNOVATIVE GOVERNANCE MODELS FOR EMERGING TECHNOLOGIES 136, 142-47 (Gary E. Marchant et al. eds., 2013); Ramachandran et al., *supra* note 246, at 1359-60.

260. *Coordination of the NNI*, U.S. NAT'L NANOTECHNOLOGY INITIATIVE, <http://www.nano.gov/about-nni/what/coordination> (last visited Sept. 17, 2014).

biology.²⁶¹ This could consist of a multi-agency coordinating committee within the federal government to develop consistent and coordinated research, technology assistance, and regulatory goals and approaches.

A slightly different and narrower institutional innovation would be to create an international scientific advisory board to study and provide periodic assessments of the scientific data on the benefits, risks, and uncertainties associated with synthetic biology. This body would provide an authoritative, scientific snapshot that could be used as common ground by regulators, legislators, industry, NGOs, and journalists to anchor their activities on synthetic biology. Leading scientists involved in studying synthetic biology safety are currently being called upon to provide their advice to a multitude of different forums and efforts, but centralizing the scientific assessment in one entity would provide for economy of scale by enabling all leading scientists to participate in the scientific assessment in a more efficient and streamlined approach.²⁶² Since synthetic biology raises many of the same risk issues in countries all over the globe,²⁶³ it would also make sense to make this scientific-assessment body international in scope and membership. If nations base their policies on the same scientific assessments, they are more likely to adopt consistent regulatory programs.²⁶⁴ Similar international scientific-assessment entities have been created for assessing climate change (Intergovernmental Panel on Climate Change (“IPCC”))²⁶⁵ and biodiversity (Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services),²⁶⁶ and have been proposed for other emerging technologies such as nanotechnology.²⁶⁷

Another useful initiative might be some sort of private-public partnership to develop the data and risk assessment models that agencies such as the EPA

261. Marchant & Wallach, *supra* note 259, at 147–52 (proposing a “Governance Coordinating Committee” for synthetic biology). The President’s Commission also called for greater central coordination of oversight responsibilities for synthetic biology, but proposed that such a coordinating function could be implemented through existing institutions such as the White House Office of Science and Technology Policy, rather than through the creation of new agencies or oversight bodies. PRESIDENTIAL COMM’N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 127.

262. See Anderson et al., *supra* note 198, at 589.

263. See Zhang et al., *supra* note 6, at 11.

264. LINDA BREGGIN ET AL., SECURING THE PROMISE OF NANOTECHNOLOGIES: TOWARDS TRANSATLANTIC REGULATORY COOPERATION 89 (2009), available at http://www.chathamhouse.org/sites/default/files/public/Research/Energy,%20Environment%20and%20Development/ro909_nanotechnologies.pdf.

265. See generally Bruce Tonn, *The Intergovernmental Panel on Climate Change: A Global Scale Transformative Initiative*, 39 FUTURES 614 (2007) (detailing the role of the IPCC and how it has been successful).

266. Emma Marris, *UN Body Will Assess Ecosystems and Biodiversity*, 465 NATURE 859, 859 (2010).

267. See Gary E. Marchant & Andrew White, *An International Nanoscience Advisory Board to Improve and Harmonize Nanotechnology Oversight*, 13 J. NANOPARTICLE RES. 1489, 1495–97 (2011) (discussing the benefit of an international nanoscience advisory board).

need to provide effective regulatory oversight. While statutes such as TSCA do have various deficiencies as outlined above, the biggest impediment agencies are likely to face with synthetic biology are the uncertainties and novelty in trying to assess product risks. All synthetic biology products are unlikely to be dangerous and thus across-the-board restrictions are likely to do more harm than good. Rather, agencies need the capability to identify the products and scenarios most likely to present significant risks and to identify risk management options that can adequately control those risks. To achieve this, agencies need better data and risk assessment methods. Given that it is also in industry's interest for the government to develop this more fine-tuned and effective regulatory focus,²⁶⁸ there should be opportunity and common interest in industry and government pooling their expertise and resources to develop the tools necessary to better predict and manage synthetic biology risks proactively. A relevant precedent might be the NanoSafety Consortium for Carbon ("NCC"). The NCC is a voluntary industry association with the objective of working with the EPA to generate knowledge and safety data that will enable the EPA to administer a more informed, effective, and efficient oversight scheme of carbon nanotechnology products.²⁶⁹

As with synthetic biology, the impetus for the creation of the NCC was the lack of validated screening tests for a new category of products that needed to be reviewed by the EPA under section 5 of the TSCA.²⁷⁰ The standard screening tools that the EPA uses for new chemicals under section 5, such as structure activity relationship analysis,²⁷¹ were not applicable to nanotechnology (or synthetic biology) because toxicity or risk is not based primarily on the chemical structure of the product. Given the lack of simple screening tests and the substantial uncertainties about nanotechnology risks (or even how to test for them), the EPA had no alternative but to review such products in a resource- and time-intensive, case-by-case manner.²⁷² This approach, while necessary at this time, potentially imposes burdensome and

268. Companies producing products that must receive regulatory approval benefit from the stability and certainty that an evidence-based regulatory system provides. For example, if a company produces a product that imposes unreasonable risks that are not detected during regulatory approval, the producer of that risky technology may benefit in the short-term, but in the long-term will likely be adversely affected by costly recalls, liability, and damage to its reputation and brand name.

269. NANOSAFETY CONSORTIUM FOR CARBON, <http://www.nanosafetyconsortium.com/> (last visited Sept. 17, 2014). For example, one of the most common categories of carbon nanotechnology materials are carbon nanotubes, which are very thin cylindrical forms of carbon that have "unique strength, electrical, and thermal properties" that the EPA could learn more about through working with a multi-disciplinary association as discussed above. See *Glossary*, U.S. NAT'L NANOTECHNOLOGY INITIATIVE, <http://www.nano.gov/about-nni/glossary> (last visited Sept. 17, 2014).

270. John C. Monica, Jr., *An Industry-Driven Approach to EHS Issues: "The NanoSafety Consortium for Carbon,"* 7 NANOTECHNOLOGY L. & BUS. 254, 258-60 (2010).

271. See *supra* note 156.

272. *Id.* at 258-59.

perhaps duplicative testing requirements on each new product and creates a substantial regulatory bottleneck.²⁷³ In response to prodding from the EPA, 12 companies in the industry grouped together to create the NCC.²⁷⁴ They developed the NCC to work with the EPA and leading scientists to develop a mutually agreeable test program for a representative set of carbon nanomaterials. The program intended to reduce testing costs while nevertheless providing the EPA sufficient data to make informed decisions.²⁷⁵ To build public trust, the NCC is committed to transparency and independence, using the best sources of scientific information and publishing all results, favorable or not, in the open literature.²⁷⁶ A similar model could be developed for synthetic biology products: companies planning to submit new products to the EPA for approval under TSCA section 5 could work with the EPA and independent scientists in a voluntary program to develop data sets and test methods that could be used to streamline the EPA review of synthetic biology products. This type of program could provide a win-win solution whereby industry can be assured of a less burdensome and speedier product approval system while at the same time the EPA has better tools and data to ensure public safety.

Finally, although this Article has primarily focused on specific regulatory instruments and approaches, mention must be given to the importance of public opinion concerning the future prospects for synthetic biology.²⁷⁷ Public opinion can play a critical role in the progress of synthetic biology—public confidence in the oversight of the technology can help assure the success and many potentials of synthetic biology, whereas public mistrust and fears can seriously impede development of the technology, as was the case with genetically modified foods in Europe.²⁷⁸ There is widespread recognition that public and stakeholder engagement must be built into any oversight system, but designing and structuring such opportunities for effective and meaningful public participation remain a major challenge.²⁷⁹

CONCLUSION

As indicated by the discussion above, the EPA's ability to adequately regulate synthetic biology microbes will be substantially dependent on the

273. *Id.* at 257–59.

274. NANOSAFETY CONSORTIUM FOR CARBON, *supra* note 269.

275. Monica, Jr., *supra* note 270, at 259–61.

276. *Id.* at 260–61.

277. See Jennifer Kuzma & Susanna Priest, *Nanotechnology, Risk, and Oversight: Learning Lessons from Related Emerging Technologies*, 30 RISK ANALYSIS 1688, 1694–96 (2010).

278. INT'L RISK GOVERNANCE COUNCIL, *supra* note 3, at 37–39; Jim C. Philip et al., *Synthetic Biology, the Bioeconomy, and a Societal Quandary*, 31 TRENDS IN BIOTECHNOLOGY 269, 270–71 (2013).

279. INT'L RISK GOVERNANCE COUNCIL, *supra* note 3, at 38–39; UNDERSTANDING RISK: INFORMING DECISIONS IN A DEMOCRATIC SOCIETY 133–54 (Paul C. Stern & Harvey V. Fineberg eds., 1996) (discussing challenges and approaches to implementing changes).

EPA's ability to assess the risks of new synthetic biology organisms. This is an extremely daunting task. Currently, the EPA generally evaluates the risks of a new organism based upon the known relatives of that organism.²⁸⁰ This method may be insufficient for synthetic biology microbes, given that such microbes may be derived from a large number of existing organisms, with no particular organism providing a close enough relative for pertinent risk assessment purposes. Further, the manner in which the EPA has evaluated traditionally genetically engineered microbes depends significantly on the presumption that the basic biology of the microbe has not changed through 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 the EPA's analyses.²⁸¹

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. 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.²⁸² These challenges, however, can also represent opportunities—opportunities to revise and realign a regulatory structure so as to provide more efficient and more comprehensive risk protection. Addressing the regulatory concerns surrounding synthetic biology microbes early and proactively can permit synthetic biology to continue to develop in as rapid a manner as possible while adequately protecting human health and the environment.

280. PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, *supra* note 2, at 131; RODEMEYER, *supra* note 5, at 26.

281. See Tucker & Zilinskas, *supra* note 21, at 35–37.

282. See generally Mandel, *supra* note 39.