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Evaluation of Regulatory Framework for Algae and Cyanobacteria Engineered to Produce Transportation Fuels

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I. Introduction

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 many limitations and problems, including loss of ecosystems, increases in food prices, and producing limited or even negligible environmental benefits over their lifecycle.[1] Accordingly, second and third generation biofuels produced from non-food biomass are being pursued as a more sustainable, long-term solution,[2] and single-cell algae (or microalgae) and cyanobacteria (or blue-green algae) (referred to collectively in this paper as "algae") are one of the leading candidates for the production of biofuels. 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.

A critical issue for the use of synthetic biology to produce new biofuels is the regulatory framework for these products that will provide assurance of safety while not unduly burdening this nascent technology. The primary regulatory oversight of algae modified by synthetic

[1] Asha Parmar et al., *Cyanobacetria and Microalgae: A Positive Prospect for Biofuels*, 102 BIORESOURCE TECH. 10163, 10163 (2011).
[2] Miguel A. Carriquiry, Xiaodong Du and Govina R. Timilsina, *Second Generation Biofuels: Economics and Policies*, 39 ENERGY POLICY 4222, 422 (2011); Jasvinder Singh and Sai Gu, Commercialization Potential of Microalgae for Biofuels Production, 14 RENEWABLE & SUSTAINABLE ENERGY REVIEWS 2596, 2597 (2010).

biology (referred to in this paper as "SB algae") will be provided by the U.S. Environmental Protection Agency ("EPA") under the Toxic Substances Control Act ("TSCA"). This paper critically analyzes the regulatory framework under TSCA for SB algae. It begins in Part II by describing algae and cyanobacteria, evaluating how they might be modified using synthetic biology to produce biofuels, describing how such SB algae might be cultivated and harvested, and evaluating potential scenarios for exposure and risks to humans or the environment. Part III then summarizes the regulatory framework that will apply to SB algae under TSCA, and addresses some generic applicability issues in TSCA's potential application to SB algae. Part IV considers and evaluates the regulatory oversight provided by TSCA over the life-cycle of SB algae, identifying potential gaps and shortcomings in the TSCA regulatory framework as applied to SB algae.

II. Background on Microalgae and Cyanobacteria

A. Advantages of Algae and Cyanobacteria for Biofuel Production

Microalgae and cyanobacteria are single-cell organisms that capture sunlight through photosynthesis and use the stored energy to convert inorganic substances into simple sugars.[3] Despite many similarities, there are some significant differences between microalgae and cyanobacteria. For example, unlike algae, cyanobacteria do not naturally produce oils.[4] Another important difference is that algal cells must be destroyed to extract their products, while cyanobacteria secrete their products into the inter-cellular media, greatly simplifying the

[3] National Renewable Energy Laboratory (NREL), A Look Back at the U.S. Department of Energy's Aquatic Species Program—Biodiesel from Algae 2 (1998); Parmar et al., *supra* note 1, at 10164.
[4] Parmar et al., *supra* note 1, at 10164.

extraction process.[5] Despite these differences, as the primitive ancestors of modern plants, algae and cyanobacetria have relatively simple cellular systems, and as a result they can devote virtually all their cellular resources to the conversion of solar energy into biomass. Additionally, the lack of multicellular structure allows algae and cyanobacetria to remain in aqueous suspension where their cellular surface area has maximum contact with nutrients such as CO_2.[6] These advantages over complex plant species give algae the ability to generate superior quantities of biomass per unit of land. Cyanobacteria and algae can convert as much as 10 and 5 percent, respectively, of the sun's energy into biomass, compared to 1 percent by traditional energy crops such as corn or sugarcane.[7]

In recent years there has been a surge of interest in utilizing algae for renewable fuel production, catalyzed by policy objectives to reduce reliance on foreign energy and to slow the increases in greenhouse gas emissions. 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 (natural oil)."[8] 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.[9]

These biofuels provide many environmental benefits – for example, "[b]iodiesel performs as well as petroleum diesel, while reducing emissions of particulate matter, CO,

[5] Neil Savage, *Algae: The Scum Solution*, 474 NATURE S15, S16 (2011.)
[6] NREL, *supra* note 3, at 3.
[7] Parmar et al., *supra* note 1, at 10163.
[8] NREL, supra note 3, at 3.
[9] Savage, *supra* note 5, at S16; Parmar et al., *supra* note 1, at 10164.

hydrocarbons and SOx. Emissions of NOx are, however, higher for biodiesel in many engines."[10] Through their photosynthetic metabolism, algal cells take in carbon dioxide and release oxygen as a metabolic byproduct. This carbon sequestration quality 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, biofuel made from algae is nearly carbon neutral.

The high production capability of algae make them an attractive source for biofuels. Algae can proliferate at a very rapid rate, and can accumulate high concentrations of oils or other feedstocks that can be used for fuel or fuel production.[11] Under favorable growth conditions, some algae species can accumulate as much as 50 to 70 percent of their dry weight in the form of oils.[12] This tremendous production potential would enable algae to produce up to 58,700 liters of oil per hectare of cultivation, which is one to two magnitudes higher than what is possible from other energy crops.[13] Algae grow to high densities and have high per-acre productivity, providing for efficient mass cultivation.[14] 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.[15]

B. Potential Role of Synthetic Biology

[10] NREL, *supra* note 3, at7.
[11] Chun-Yen Chen, et al., *Cultivation, Photobioreactor Design and Harvesting of Microalgae for Biodiesel Production: A Critical Review*, 102 Bioresource Technology 71, 71 (2011).
[12] Chen et al. *supra* note 11, at 71.
[13] Chen et al. *supra* note 11, at 71.
[14] Parmar et al., *supra* note 1, at 10164.
[15] David Biello, *The False Promise of* Biofuels, Scientific American, Aug. 2011, at 64; Parmar et al., *supra* note 1, at 10164.

Genetic engineering of algae, particularly using the more powerful techniques of synthetic biology, has enormous potential to improve biofuel production in algae and help make it economically competitive with other fuel types and sources.[16] Due to their simple structure, algae make easy targets for extensive genetic manipulation compared to higher plants. A number of helpful traits could be engineered into algae to improve their biofuel production, including traits for producing different types of hydrocarbons that could be used for improved biofuels, secreting oils into the environment so the cells don't need to be harvested to extract their products, to better utilize atmospheric CO2 as a carbon source, and to grow faster and stronger in a variety of different environments, including salt water and stressed environments.[17]

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. 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.[18] However, synthetic biology may be better capable of overcoming these barriers than traditional genetic engineering techniques. Indeed, recent news stories quote 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 needed.[19]

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[16] Biello, *supra* note 15, at 64; Parmar et al., *supra* note 1, at 10170-71.
[17] Savage, *supra* note 5, at S16; Biello, *supra* note 15, at 65.
[18] R. Raja, et al., *A Perspective on the Biotechnological Potential of Microalgae*, 34 CRIT. REV. MICROBIOLOGY 77, 85-86 (2008).
[19] Ansa Varughese, *Venter's New Hope: Synthetic Algae for Biofuels*, BioTechniques, Nov. 7, 2011, available at http://www.biotechniques.com/news/Venters-New-Hope-Synthetic-Algae-for-Biofuels/biotechniques-323264.html.

C. Environmental Releases, Exposures and Risks

The major safety and regulatory concern about SB algae will be the environmental release, exposure and risks of the engineered organisms. A key factor influencing such concerns will be whether the algae are grown in open (i.e. open pond systems) or closed (bioreactor) systems.[20] Most commercial cultivation of algae is currently carried out in open pond systems.[21] Open cultivation utilizes uncovered 'ponds' that can be either man made 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 model.[22] 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 cultivated algae may escape into the environment. Open pond systems also require larger areas of land than closed systems.[23]

The other principle cultivation model involves photobioreactors to create a closed environment for cultivation, where conditions can be monitored and controlled. Consequently, cultivation can be maximized through a careful balancing of the variables. For example, algae grown in plastic tubes in ponds provide up to seven times the productivity of open ponds.[24] Another comparative advantage of closed systems is the protection against unintended

[20] Chen et al., *supra* note 11, at 72.
[21] Chen et al., *supra* note 11, at 72.
[22] Parmar et al., *supra* note 1, at 10164.
[23] Chen et al., *supra* note 11, at 72.
[24] Singh & Gu, *supra* note 2, at 2597.

contamination or release.[25] Even with contained uses, however, the risk of accidental environmental release is not zero, although it is less than open cultivation.

If SB algae products are released accidently into the environment, there is likely to be much uncertainty about the resultant likelihood and nature of risks to the natural environment or human health. Modified SB algae could be transported through the air for long distances, and could survive a variety of harsh environments in dormant form.[26] The risks of the release of most genetically engineered organisms into the environment creates some uncertainty, and given the more substantial modifications made possible by synthetic biology, it is likely that SB products such as algae that may be released into the environment will create even greater uncertainties. Some of the uncertainties include the likelihood and rate of accidental release, the survivability of the SB algae in the surrounding environment, its ability to reproduce, spread and compete in the natural environment, and the mechanisms and magnitude of any possible risks to the environment or human health.

III. TSCA Oversight: Generic Issues and Applicability

A. TSCA Overview

Under the Coordinated Framework for Regulation of Biotechnology, EPA has primary responsibility for regulating most genetically engineered microbes under TSCA (except for microorganisms regulated by another federal agency).[27] EPA has elected to limit its regulatory

[25] NREL, supra note 3, at 5.
[26] Parmar et al., *supra* note 1, at 10170.
[27] Office of Science and Technology Policy, Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986). For a more comprehensive overview of EPA's regulation of microorganisms, see Michael Rodemeyer, Summary of Laws and Regulations Applying to the Regulation of Products of Biotechnology, at 5-7 (Oct. 24, 2011 draft).

review to intergeneric microorganisms created by the transfer of DNA between organisms of different taxonomic genera for commercial purposes.[28] Unless otherwise exempted by EPA regulations, manufacturers of new intergeneric engineered microorganisms must submit a Microbial Commercial Activity Notice ("MCAN") to EPA for review at least 90 days prior to the commercialization of the product. [29] This notice requirement functions as the equivalent of a pre-manufacturing notice ("PMN") for chemical substances under section 5 of TSCA. For pre-commercialization field trials of genetically engineered microbes, the manufacturer must submit a TSCA Experimental Release Application ("TERA") to EPA at least 60 days prior to commencing field testing.

While these pre-market notification requirements of TSCA have been the primary focus of EPA's oversight of genetically engineered microbial products to date, various other provisions of TSCA could also apply to genetically engineered microbes, including SB algae, in appropriate circumstances. Before evaluating (in the next section) the application of the pre-market notification and other requirements of TSCA to SB algae, two threshold applicability issues are considered here – namely, whether living microorganisms such as SB algae are subject to TSCA, and how the intergeneric restriction on EPA's regulatory authority might affect SB algae.

B. Are Living Microbes "Chemical Substances" Regulated under TSCA?

TSCA was enacted to regulate the release of "chemical substances" into the environment.[30] When enacted in 1976, Congress gave no indication that it anticipated the

[28] EPA, Microbial Products of Biotechnology; Final Regulations under the Toxic Substances Control Act; Final Rule, 62 Fed. Reg. 17,910, 17913 (April 11, 1997).
[29] The EPA regulations for the MCAN and TERA contain a number of full or partial exemptions which are unlikely to apply synthetic biology-produced microbes, and thus are not discussed here. Likewise, the regulations only apply to product development with an immediate or eventual commercial intent, which likely includes all or most synthetic biology-produced microbes.
[30] 15 U.S.C. § 2601 .

inclusion of living microorganisms within the definition of "chemical substance."[31] However, in adapting TSCA to regulate biotechnology products, EPA concluded over twenty-five years ago that Congress intended "chemical substance" to be defined broadly to encompass living microorganisms.[32] EPA's definition of "chemical substances" to include living microorganisms has not been challenged over the decades in which the agency has been regulating biotechnology. However, to the extent that synthetic biology creates new regulatory controversies under TSCA, it may lead to a challenge to EPA's regulation of living microorganisms under TSCA.

There is academic commentary questioning TSCA's reach to living microorganisms.[33] The statute defines "chemical substance" as "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 . …"[34] The strongest argument against EPA's determination is that living microorganisms do not generally have a "particular molecular identity." EPA would likely counter that Congress defined the term "chemical substance" broadly and non-inclusively, and moreover 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." It is likely that EPA's definition would prevail in a legal challenge under the *Chevron* doctrine which requires reviewing courts to defer to an agency's "reasonable" interpretation of

[31] Robin A. Chadwick, *Regulating Genetically Engineered Microorganisms Under the Toxic Substances Act*, 24 HOFSTRA L. REV. 223, 234-35 (1995).
[32] EPA, *supra* note 28, at 17,913-14; EPA, Microbial Products of Biotechnology: Final Regulation Under the Toxic Substances Control Act – A Summary of the Public's Comments and the Agency's Response, at 8-12 (Mar. 26, 1997).
[33] Louis S. Sorell, *Biotechnology Regulation Under the Toxic Substances Control Act*, 3 PACE ENVTL. L. REV. 57, 63-65 (1985).
[34] 15 U.S.C. § 2602 (2).

an ambiguous statutory provision.[35] However, if challenged, there is a possibility that EPA's approach would be invalidated by the courts, leaving EPA without any statutory authority to regulate modified microorganisms. Moreover the mere possibility of such an outcome may deter the EPA (at least at the margins) from regulating aggressively and possibly prompting a legal challenge to its jurisdiction.

D. *Inter-generic Limitation*

As described above, EPA has limited its regulatory authority to inter-generic modified microorganisms. Synthetic biology may create some difficulties for this EPA policy. Traditional genetically modified microorganisms involve the transfer of genetic information from one organism to another. EPA's policy is based on the premise that the transfer of genetic information from more distantly related organisms (i.e., from different genera) are more likely to create new or modified traits that could present a risk.[36] This regulatory approach seems to have been successful to date. Thirty-two MCANs for inter-generic genetically modified microbes, of which one was withdrawn by the submitter, and all the others were allowed to go forward (although in one case subject to a significant new use rule (SNUR)).[37] Of the 31 MCANs allowed to go forward to commercialization, EPA has received a Notice of Commencement (NOC), required to indicate the date the microorganism is entered into commerce, for 15 of these modified microbes.[38] EPA has also received 23 TERAs, of which 21 have been approved, one was suspended pending additional information, and one was rejected as invalid.[39] For both the inter-generic microorganisms subject to the MCAN and/or TERA procedure, as well as the

[35] Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984).
[36] EPA, *supra* note 28, at 17,914.
[37] EPA, Biotechnology Program Under the Toxic Substances Control Act (TSCA), Notifications, FY 1998 to Present (undated, available at http://epa.gov/biotech_rule/pubs/submiss.htm.
[38] *Id.*
[39] *Id.*

unknown number of intra-generic modified microbes immune from regulation, there have been no reported problems to date.

Synthetic biology has the potential to create new complications and problems under this existing policy. While traditional genetic engineering involves the transfer of genetic information essentially as it exists in another organism, synthetic biology creates the opportunity to change parts of the genetic material by customizing parts of the DNA to sequences that may not exist in nature. Thus, for example, scientists may remove the DNA from an existing organism, modify the DNA, and then re-insert that DNA back into the same organism. Since this would not involve the inter-generic transfer of genetic information, it would not be subject to the EPA's notification requirements, even though the modified DNA may have a greater probability of creating a novel risk than most inter-generic transfers subject to regulation. Other complications could also arise. If some of the DNA changes designed into the host microbe using synthetic biology happened to correspond fortuitously to DNA sequences in organisms in other genera, would this trigger the regulatory requirement/to submit a MCAN? While it is unlikely that a single base pair mutation would qualify as an "inter-generic" transfer, it is not clear how many small changes would have to be made to reach that threshold.

Further into the future, the sequence of inserted synthetic DNA may be entirely non-natural, having no basis in any existing organism's DNA. But because the novel DNA is not from an existing organism, the transfer is not inter-generic, and so would not be subject to EPA's regulatory authority under existing policy. Similarly, if the host microbe that will be used to engineer in specific functional genes to form a new microbial product intended for commercial purposes and hence potentially subject to TSCA was itself created previously by synthetic biology and had no known "parent" organism or genus (i.e. constructed from genetic sequences

from multiple microbes), it may not make any sense to talk about an inter-generic transfer. These potential complications may force EPA to reconsider its inter-generic restriction in order to provide effective oversight of synthetic biology products such as SB algae.

IV. Applying TSCA Across the Life-Cycle of SB Algae

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

A. R&D

At the research and development stage, the developer of an SB algae strain must submit a TSCA Experimental Release Application ("TERA") to EPA at least 60 days prior to any field testing of a new strain. EPA will then have 60 days to review that submittal. A key challenge for this field testing requirement for all genetically engineered microbes, including SB algae, is that any risks that escape 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 chemical substances, where the problem is limited to the usually small quantity of chemical used in the field test. At the same time, because many products in the R&D stage are not successful and may never be commercialized, imposing significant regulatory costs and burdens at this early stage of product development would have adverse impacts on innovation. Therefore EPA must strike a delicate (and inevitably not always optimal) balance

between precaution and innovation in implementing the TERA review. The increased uncertainties about the risks from SB algae relative to "traditional" genetically modified microbes will exacerbate this tension.

The TERA provision also excludes research that is not intended to result in a commercial product.[40] This exclusion was derived from TSCA section 5(i) which limits all TSCA section 5 screening to commercial activities.[41] Yet, unlike traditional chemical substances regulated by TSCA, a small amount of a living engineered organism, capable of reproducing and spreading, has the potential to still cause significant harm. As EPA itself recognized in adopting this approach, "there are no differences in risk depending on funding source."[42] Thus, even though most synthetic biology research will meet the definition of commercial research subject to TSCA, the possibility that some research will escape such review and could potentially cause widespread problems may require reconsideration of this exclusion for non-commercial research.

A related challenge is how thoroughly and effectively EPA can identify and address any risks created by field testing of SB algae products in the 60 day window provided to the agency under the TERA process. Unlike other products such as chemicals that can be quickly evaluated by models such as structure-activity relationships ("SAR"), there are no such screening methods for SB products. 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, EPA's capability to reliably assess risks of field testing SB algae in the 60 days provided by the TERA process is questionable.

[40] 40 C.F.R. § 725.205.
[41] EPA, *supra* note 28, at 17,922.
[42] *Id.* at 17,923.

Another possible issue at the R&D stage is that the TERA requirement includes an exception for certain enclosed uses.[43] As discussed above, SB algae can be grown in open or enclosed systems. Given the increased complexity and uncertainty about risks that SB products may present, there may need to be a reconsideration of whether contained field tests of SB products should be exempted from the TERA requirement. On the other hand, such an exemption may provide an incentive for product developers to plan on contained field tests, which are likely to be the safest option. Another issue specific to synthetic biology is that some products may include biological containment systems that will 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.[44] The National Institutes of Health (NIH) has developed more detailed biological containment requirements as part of its recombinant DNA guidelines,[45] which may serve as a useful model for EPA. It may be appropriate to revise the TERA regulations to better elaborate and encourage such additional safety measures.

B. Pre-Commercial Notification

The most significant regulatory control EPA will have under TSCA for SB algae is at the pre-commercialization notification stage, but even this authority is quite limited and could be problematic if SB algae presents significant risks. The developer of a new SB algal strain involving the transfer of DNA from an organism from another genus must submit a Microbial Commercial Activity Notice ("MCAN") to EPA at least 90 days prior to commercialization. EPA then has 90 days to make a determination on whether the product will present an

[43] 40 C.F.R. § 725.234
[44] 40 C.F.R. §§ 725.3, 725.234.
[45] National Institutes of Health, NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix I:Biological Containment (May 2011).

unreasonable risk to human health or the environment. Like the PMN requirement on which it is derived from section 5 of TSCA, the MCAN imposes no affirmative duty on the product developer to generate any safety data, but rather only requires the developer to submit whatever data it has in its possession.

There may be concerns that EPA lacks sufficient authority to provide a meaningful safety review in 90 days with no mandatory data requirements, and such concerns will be even greater for SB algae. Unlike chemicals, which EPA usually evaluates using SAR modeling, EPA lacks any existing methodology or data set against which to evaluate the risks of novel SB algae products. Moreover, while PMN analyses for chemicals focus on human toxicity, most risk scenarios for SB algae involve environmental releases that result in some form of ecological harm, which are much more difficult to study and predict than human health risks. Accordingly, there are serious doubts about EPA's ability to identify and manage any risks that may be presented by SB algae using the existing MCAN mechanism.

Notwithstanding the serious limitations on EPA's authority under section 5 of TSCA, EPA has been innovative in leveraging that authority to engage product manufacturers in a more proactive and collaborative set of safety measures. A good example is how EPA has used its section 5 authority for nanomaterials, which have some similarities to SB algae in that they present greater uncertainties about risk that are not amenable to being addressed using modeling techniques such as SAR. EPA has nevertheless used its section 5 authority to persuade product manufacturers to enter into consent decrees in which they agree to undertake additional safety measures such as various worker protection measures (e.g,, use of personal protective equipment), conducting sub-chronic toxicity studies on the products, and imposing restrictions on product use. A similar approach could be developed for SB algae and other synthetic biology

products that might come under 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 SB algae primarily involve potential ecological rather than human health risks, this might be a more difficult undertaking than was the case for EPA's treatment of nanomaterials.

Finally, despite the limitations, the MCAN requirement is EPA's most effective and powerful regulatory tool for ensuring the safety of SB algae. It will be necessary for EPA to bulk up this program with additional staff, resources, expertise and research if it is to use its authority effectively to oversee SB algae and other innovative microbial products in the pipeline.

C. Safety Testing

If EPA determines that more safety data are needed for an SB algae product, it has authority under section 4 of TSCA to require the product manufacturer to conduct and report the necessary testing. However, this authority is subject to several conditions that have limited the effectiveness of this statutory provision for chemicals, and may be even more problematic for SB algae. The dilemma for EPA is that it can only require testing of a product after the agency has sufficient data to meet its burden under section 4 to show there may be a problem and a need for testing.

Specifically, under section 4, EPA must make a series of findings before it can require a product developer to conduct testing. First, the agency must find that either (1) the product may present an "unreasonable risk of injury to health or environment"; or (2) 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."[46] Second, EPA must find

[46] 15 U.S.C. § 2603(a)(1)(A)(i), (B)(i).

that existing available data are "insufficient" to determine or predict the health and environmental effects of the product.[47] Finally, EPA must find that testing is "necessary to develop such data."[48]

These requirements put a substantial evidentiary burden on EPA before it can require a product manufacturer to conduct testing. It often takes EPA approximately ten years from start to finish to adopt and implement a test rule under TSCA section 4.[49] The first finding is often the biggest obstacle for such a test rule, and this will likely also be the case for SB algae. 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 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. Accordingly, EPA almost always supports section 4 test rules using the second trigger – i.e., 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."

This required finding of substantial production, environmental release and exposure may be appropriate for chemical substances, but is not the relevant test for SB algae. Many commercial chemicals are produced in substantial quantities and are expected to be used in products and applications that result in substantial environmental release and human exposure. For example, in one of the leading TSCA section 4 test rule cases involving the chemical cumene, EPA found substantial potential for environmental release and human exposure based on a finding that an estimated 3 million pounds of cumene are released into the environment each

[47] 15 U.S.C. § 2603 (a)(1)(A)(ii), (B)(ii)..
[48] 15 U.S.C. § 2603 (a)(1)(A)(iii), (B)(iii).
[49] GAO, Chemical Regulation: Comparison of US and Recently Enacted European Union Approaches to Protect Against the Risks of Toxic Chemicals 20 (2007).

year, potentially exposing 15-16 million people.[50] For SB algae, however, the assumption of substantial environmental release and human exposure is not valid. The expectation will be that SB algae will be controlled and contained, and thus if substantial environmental release and human exposure occurs, the regulatory and risk management systems will have already failed. Or in other words, EPA could not mandate safety testing of SB algae until it is too late and the algae have escaped their containment. Testing at that point can help determine what the risks are likely to be, but is largely irrelevant to the central purpose of the regulatory oversight system in preventing uncontrolled environmental release from occurring in the first place. Thus, as currently structured, the TSCA section 4 test program criteria does not provide an effective tool for SB algae, where some type of hazard determination may be needed prior to environmental release precisely for the purpose of designing a containment system that will provide appropriate prevention of any potentially dangerous environmental release.

D. Post-Market Surveillance and Risk Management

TSCA also provides authority for EPA to conduct post-market surveillance and risk management of regulated products such as SB algae, although with mixed effectiveness. Section 8 of TSCA provides a series of reporting and recordkeeping requirements, some of which could be important for oversight of SB algae. For example, section 8(c) requires the manufacturer or distributor of a product to keep records of significant adverse effects to human health or the environment alleged to have been caused by their product. EPA regulations limit such record-keeping 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);

[50] Chemical Manufacturers Ass'n. v EPA, 899 F.2d 344, 348 (5th Cir. 1990).

(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."[51] Several of these triggers would presumably apply to any accidental environmental release of, or adverse effects from, SB algae, 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. Second, the company is only required to retain the information and is not required to report the allegations to EPA unless specifically requested to do so.

Section 8(e) of TSCA requires the manufacturer or distributor of a product to report to 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." EPA has not issued regulations implementing section 8(e) to date, so it is not clear precisely what type of scenarios relating to SB algae 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 EPA about SB algae, such as unintended environmental releases that may not trigger section 8(e) but which may be of concern to EPA.

[51] 40 C.F.R. § 717.12(c).

IF EPA identifies potential post-marketing risks associated with SB algae, it potentially could take regulatory action under section 6 of TSCA to manage those risks. Section 6 of TSCA gives EPA an extensive menu of potential risk management options including a 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.[52] However, to impose such a requirement, EPA must make a finding based on a risk/benefit calculation that the product poses an "unreasonable risk," and moreover that the proposed regulatory action is the least burdensome for protecting against the unreasonable risk.[53] As enforced by the courts, these requirements are very burdensome for the agency to satisfy.[54] Indeed, 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), and one of those rules (asbestos) was subsequently over-turned in court.[55] If EPA cannot support a section 6 rule for a known "bad actor" like asbestos, for which hundreds of toxicological studies exist and thousands of deaths have been attributed, it is unlikely to have the necessary evidentiary support to regulate a product like SB algae under section 6 where there are limited data and substantial uncertainties about the risks. This then represents a major gap for the regulatory oversight of SB algae under TSCA – if a risk exists and EPA fails to identify and address that risk in the brief MCAN window of opportunity, the agency may be without any effective regulatory authority to manage those risks.

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[52] 15 U.S.C. § 2605(a).
[53] 15 U.S.C. § 2605(c)(1).
[54] Corrosion Proof Fittings v. EPA, 987 F.2d 1201 (5th Cir. 1991).
[55] GAO, Chemical Regulation: Options Exist to Improve EPA's Ability to Assess Health Risks and Manage Its Chemical Review Program (2005).

E. Disposal

The final stage of the product life cycle is disposal, which could represent a significant risk scenario for SB algae. If large quantities of algae are processed to produce fuels, the residual biomass must be disposed of in some manner, and will likely 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. 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, making it unlikely they will ever be imposed for SB algae (or any other product) under the existing statutory provision. It is also possible that EPA could utilize other statutory authority to regulate SB algae waste, such as the RCRA hazardous waste program, but that would likely require EPA to list such wastes as hazardous wastes.[56]

The Clean Water Act (CWA) could also potentially apply to SB algae. The CWA defines "pollution" broadly to include "the man-made or man-induced alteration of the chemical, physical, biological, and radiological integrity of water" and the term "pollutant" specifically includes "biological materials."[57] Discharges of algae (whether modified or not) would therefore be considered pollution under the CWA. There are two limitations under the CWA however that may limit the applicability of the statute to algal operations. First, the CWA only applies to water bodies that have a "significant nexus" to navigable waters, a limit that may exclude isolated ponds used to grow algae from regulation. However, any significant effluent runoff

[56] 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 EPA. SB algae wastes would likely not meet any of the characteristics, so would have to be listed to be designated as hazardous. 490 C.F.R. part 261, Subpart C&D.

[57] 33 U.S.C. § 1362(6), (19)..

from such ponds or operations would be potentially subject to regulation.[58] The second limitation is that the CWA only regulates in any significant way discharges from "point sources," which does not include non-point sources such as runoff from agricultural or other dispersed activities. Finally, even if SB algae operations resulted in the significant release of algae into navigable waterways from a point source, it is unlikely that SB algae would be regulated any differently than other algae under the CWA.

Conclusion

The Toxic Substances Control Act is the most applicable and relevant statutory program for regulating any potential health and environmental risks from SB algae. The centerpiece of TSCA's oversight as applied to SB algae will be the pre-manufacturing notice requirement provided by the MCAN requirement. Under this procedure, EPA will have the opportunity to review and take regulatory action on any new SB algae product before it can be commercialized. However this regulatory authority has several serious limitations. First, EPA has only a short time to review the MCAN submissions, and there is no requirement that the submitter generate any information on risks associated with the product. The complexity of SB algae, combined with the lack of any applicable toxicological screening method, will make it very difficult for EPA to thoroughly evaluate and mitigate any risks from SB algal products in the 60 day MCAN review period. This challenge will be intensified by the likelihood that any significant risks from SB algae are likely to be ecological risks, which are harder to predict ex ante. The MCAN requirement may also not apply to SB algae at all if the product does not involve the inter-

[58] Rapanos v. United States, 547 U.S. 715 (2006).

generic transfer of DNA, or if EPA's policy of regulating microorganisms under TSCA as "chemical substances" is struck down by the courts as contrary to the statutory intent.

The MCAN pre-notification procedure is likely EPA's only realistic opportunity to regulate SB algal risks under the existing statute. For the reasons explained above, EPA is unlikely to be able to meet the statutory criteria for imposing testing under section 4 or risk management requirements under section 6. EPA may be able to obtain useful data from the section 8 reporting requirements, but even those may not fit well with the types of potential problems that could be associated with SB algae.

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

TSCA generally has come under a lot of criticism as an ineffective and outdated regulatory framework for regulating toxic substances generally. There is now a general 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. While there are important differences in the bills introduced to date, the general direction of the revisions is to require manufacturers of chemical substances (presumably including SB algae) to produce a minimum set of safety data before commercializing their products.[59] The proposed legislation will also ease the procedural and substantial burdens on EPA to promulgate

[59] Congressional Research Service, Proposed Reform of the Toxic Substances Control Act (TSCA) in the 112th Congress: S.847 Compared with Current Law (July 25, 2011).

risk management rules under section 6 of TSCA. These revisions, if adopted, will significantly enhance the ability of TSCA to regulate SB algae, although the precise implications for SB algae will depend on the final details of the enacted legislation.