NAVIGATING THE REGULATORY LANDSCAPE

BIOMINING CASE STUDY

Context

Copper has all manner of uses, from wiring and building materials to jewelry and consumer goods. Its extraction has always been an expensive, energy-intensive, and often inefficient process. Copper production is increasing globally, with most mining occurring in Chile, Peru, China, and the United States.

Conventional copper mining of low-grade ore entails draining a highly acidic solution through huge piles of crushed rock. The leachate is collected and processed to capture the copper by electroplating. This technique requires significant energy and chemicals and leaves behind much useable copper trapped in the tailings, the low-value rock byproduct of mining. To improve the yield of copper, some mines add natural microbes to the acid solution. These organisms are extremophiles, none of which is known to be pathogenic, and is capable of existing under more extreme conditions, such as those in the acidic leachate.

Description of the new technology

To make this process more efficient, a company plans to use synthetic biology to develop microbes to extract copper more efficiently from the ore. These novel microorganisms will be designed to increase the solubility and extraction of copper from ore that, using current technology, either could not be extracted or could not be extracted by economically-justified means (*e.g.*, when requisite energy input is considered). The result is an increase in extraction efficiency

Synthetic BIOLOGY PROJECT

for copper recovery with less loss of copper in the tailings (which would represent both an economic loss and a potential for a release into the environment). In addition to being more efficient, company officials say these novel methods are better for the environment as they reduce the amount of potentially toxic metals remaining in the tailings.

The company plans to change the microbes by modifying the genetic material to increase the microbes' efficiency in leaching specific types of low-grade ore and may seek to use the modified bacteria to recover additional copper from tailings. The leaching system occurs in a loop: Once the primary copper extraction is complete the remaining leachate is reinoculated with microbes and reintroduced at the top of an ore heap rather than being disposed and potentially contributing to environmental contamination. Because of the routine addition of new inoculant, the microbes are not engineered for maximum stability and fitness and indeed cannot survive at more neutral pH (>3). As the company looks to test and eventually use these genetically modified microbes in U.S. copper mining operations, what must they consider from a regulatory standpoint?

Discussion of the legal and procedural issues

A microbe and its DNA can be considered chemical substances subject to TSCA if either is used in a manner not excluded from TSCA (*e.g.*, as a drug or pesticide). The precise chemical identity of the synthetic gene(s) is confidential. If the genes inserted into the naturally existing, recipient organism are from organisms from the same genus as the recipient, the modified organisms can still be considered naturally occurring, therefore implicitly listed on the TSCA Inventory and no TSCA Section 5 notice would be required. If, on the other hand, the synthetic genes are not identical to a sequence that occurs in an organism in the same genus as the recipient organism or are genes from an organism of a different genus that are inserted into the recipient organism, the microbe would not be considered naturally occurring and, if not otherwise listed on the TSCA Inventory, would trigger the biotechnology reporting requirement under TSCA Section 5. Note that EPA strongly encourages *any* manufacturer of a new microorganism using synthetic DNA to contact the agency to discuss the application (*see* http://www.epa.gov/oppt/biotech/pubs/fs-001.htm).

The company is developing the modified microbe for a commercial purpose. Based on public information, it is unclear whether the microbe is eligible for a TSCA Tier I or Tier II exemption. These exemptions permit producers of modified microbes that meet the eligibility requirements to proceed to commercial production with either a ten-day notice to EPA (Tier I) or an application with a 45-day review period (for Tier II). It is unclear whether the microbe is one of the species that is eligible for these exemptions. In addition, it is unclear whether the introduced genetic material is limited in size, well-characterized, poorly mobilizable, and free of certain toxin-encoding sequences, such that it meets these aspects of the exemptions' eligibility requirements. To the extent that the use pattern may lead to release of the microbes, albeit in well-controlled, recirculated water-based leaching systems on large

metal ore piles, the use would not meet the exemptions' containment requirements, so neither the Tier I nor Tier II exemption is an option. Accordingly, if the modified microbe otherwise triggers TSCA Section 5 new chemical requirements, EPA would be of the view that the manufacturer would be required to file a Microbial Commercial Activity Notice (MCAN) with EPA at least 90 days before the first non-exempt commercial manufacture of the microbe. As an alternative, the company could submit a TSCA Experimental Release Application (TERA) which, if approved by EPA, would allow the company to conduct (R&D) field studies to obtain an enhanced scientific understanding of aspects such as the microbes' survival, migration, etc. when used in the commercial process. Such understanding could be very helpful to EPA in any subsequent review of an MCAN on the microbe.

During its review, EPA will assess the potential for risk to human health and the environment, including the potential for the microbe to survive, migrate, and out-compete other microbes in the same ecosystem; transfer genetic material with wild microbes; or be pathogenic. If EPA is satisfied that the modified microbe is not likely to pose a risk to human health and the environment, it will allow the application to be "dropped from review," meaning that EPA will take no further regulatory action and the submitter may proceed with its intended non-exempt commercial production upon the expiration of the 90-day review period. If, however, EPA identifies concerns, it has the authority to ban manufacture or import of the modified microbe or to negotiate a consent order under TSCA Section 5(e) with the submitter that typically would put in place restrictions to address the risk concern as well as testing (laboratory and/or field testing) needed to understand the microbe's risks, survival, migration, etc. EPA could also determine the need for a Significant New Use Rule (SNUR) to cap or limit the production, uses, or exposure/release to those specified in the MCAN. Of the 55 MCANs received through 2013, one was withdrawn, one was regulated through a TSCA Section 5(e) consent order, one was regulated through a rulemaking (a TSCA Section 5 SNUR), and the remaining were allowed to proceed to market without restrictions. It is not clear from the available information how many of these MCANs involved intentional environmental release (as opposed to contained use) of the microorganism. In addition, we note that only 2 of 29 valid TERAs submitted to EPA were not approved.

The legal and regulatory takeaway

EPA is authorized under TSCA to regulate microorganisms created through synthetic biology for use in biomining. This is particularly the case when synthetic sequences are used to modify microorganisms in a way that introduces genetic sequences that are not known to be identical to those known to occur in an organism in the same genus as the recipient microorganism. Such genetically modified microbes would be considered new chemical substances subject to review under TSCA Section 5. EPA has a record of reviewing and regulating biotechnology products that is similar to its decisional record on regulating conventional chemicals:

- 95 percent of intergeneric microorganisms that have been the subject of MCANs have proceeded

to commercial distribution without restriction;

- 93 percent (27 of 29 applications) of intergeneric microorganisms that have been the subject of TERAs have been approved; and
- 93 percent of conventional chemicals subject to Premanufacture Notification (PMN) have not been regulated via a Section 5(e) order or a SNUR (an additional 5 percent have been voluntarily withdrawn by the notifier, often in the face of possible EPA action).

Biomining, however, could represent a use and involve a microbial species not previously considered by EPA. These factors combined with environmental releases that, given the size of mining operations, could be considered large, environmentally consequential, and ongoing are likely to present novel issues to the TSCA biotechnology program. These complex issues have the potential to attract close EPA scrutiny that would, at a minimum, likely necessitate voluntary suspensions of the review period, delay the decisional process, and increase the likelihood that EPA would determine the need to apply testing requirements to improve its understanding of potential risk aspects and/or controls on the use. If use of a modified microorganism contributed to economic and environmental benefits (*e.g.*, greater recovery of copper, and reduced residual releases to the environment of a toxic metal), these points would be important to discuss and document in a Pollution Prevention Information page attachment to the MCAN.

One Woodrow Wilson Plaza
1300 Pennsylvania Ave., N.W.
Washington, DC 20004-3027
T 202/691/4000
F 202/691/4001
www.synbioproject.org