United States Environmental Protection Agency

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Microbial Products of Biotechnology
Summary of Regulations under the Toxic Substances Control Act

EPA regulations for implementing its review program for new intergeneric microorganisms under section 5 of the Toxic Substances Control Act (TSCA) are found in the in the Code of Federal Regulations at 40 CFR part 725. These regulations tailor to microorganisms the screening program that has been in place since 1986 under the Coordinated Framework for Regulation of Biotechnology (June 26, 1986, 51 FR 23302) for microbial products of biotechnology. The regulations also define a number of exemptions and codify EPA's approach to research and development (R&D) for microbial products of biotechnology. These rules are designed to ensure that EPA can adequately identify and regulate risk associated with microbial products of biotechnology. This fact sheet summarizes the key components of the regulations. For more details, please refer to 40 CFR part 725 and the Federal Register Notice announcing the regulations, published April 11, 1997 (62 FR 17910).

Microorganisms Subject to These Rules

Microorganisms subject to this rule are "new" microorganisms used commercially for "TSCA purposes," such as production of industrial enzymes and other chemicals; agricultural practices (e.g., biofertilizers); biosensors; production of biofuels, and break-down of chemical pollutants in the environment. (See 40 CFR part 725.8(c)(1)). According to EPA's rule, new microorganisms are those "intergeneric" microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc.) formed by combining genetic material from organisms in different genera. (See 40 CFR parts 725.1(a) and 725.3.) The term for this definition is intergeneric, a concept introduced initially in the 1986 Coordinated Framework. A genus (pl. genera) is a level in a taxonomic classification system based on the relatedness of organisms. EPA believes that intergeneric microorganisms have a sufficiently high likelihood of expressing new traits or new combinations of traits to be termed "new" and warrant review. Microorganisms that are not intergeneric are not considered "new," and thus are not subject to reporting under section 5 of TSCA. When defining "intergeneric microorganism," in the case of chemically synthesized genes, the Agency has followed 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 is considered intrageneric and thus not new. 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 which case, the resulting product is considered intergeneric. EPA strongly encourages any manufacturer of a new microorganism using synthetic DNA to contact the Agency.

Reporting Requirements

The TSCA section 5 notification specifically required for microorganisms is the Microbial Commercial Activity Notice (MCAN) (40 CFR part 725 subpart D). Persons intending to manufacture or import intergeneric microorganisms for commercial purposes in the United States must submit an MCAN to EPA at least 90 days before such manufacture or import. EPA has 90 days to review the submission in order to determine whether the intergeneric microorganism may present an unreasonable risk to human health or the environment. If EPA makes that determination, EPA may impose appropriate regulatory restrictions on the microorganism.

The regulations also cover intergeneric microorganisms used in R&D for commercial purposes. The TSCA section 5 notification required for R&D testing of new microorganisms that are released in the environment is the TSCA Experimental Release Application (TERA) (40 CFR part 725 subpart E, sections 725.250-725.288). A TERA must be submitted to EPA at least 60 days prior to initiating such field trials. The TERA is designed, in recognition of the needs of researchers, to provide a high measure of flexibility and a shorter review period (60 days). R&D for commercial purposes are those activities that are funded directly, in whole or in part, by a commercial entity, regardless of who is actually conducting the research, or which will obtain for the researcher an immediate or eventual commercial advantage.

Exemptions

EPA's biotechnology rule contains several exemptions from the requirement to submit a MCAN, if the manufacturer meets criteria defining eligible microorganisms and specified use conditions. Exemptions for research and development (R&D) are contained in subpart E. There is an R&D exemption for activities conducted inside a structure (40 CFR parts 725.234 and 725.235) and outside a structure (40 CFR parts 725.238 and 725.239). A test market exemption is provided in subpart F. Subpart G provides two exemptions limited to specified recipient microorganisms and introduced genetic material that is limited in size, well-characterized, poorly mobilizable, and free of certain sequences. The "Tier I" exemption requires certain certifications and recordkeeping while the "Tier II" exemption requires certain certifications and a notification to EPA and EPA review of specific physical containment and control technologies.

Intergeneric microorganisms used for R&D in contained structures are exempt from EPA reporting requirements, if researchers maintain records demonstrating eligibility. Researchers are exempt from this record keeping requirement when the researcher or institution is in mandatory compliance with the National Institutes of Health (NIH) "Guidelines for Research Involving Recombinant DNA Molecules." Those researchers voluntarily following the NIH Guidelines can, by documenting their use of the NIH Guidelines, satisfy EPA's requirements for R&D use in contained structures. Alternatively, researchers can utilize the exemption by documenting that they meet eligibility criteria in the regulations.

Any amount of a live genetically modified microorganism subject to TSCA reporting requirements that is transported to or from a site is unlikely to be eligible for a Tier I exemption. Anyone intending to ship such a microorganism off-site will likely need to submit either a Tier II exemption notice or an MCAN. In order to qualify for a Tier I exemption, the regulations at 40 CFR part 725.424 specify that the manufacturer must certify that they meet all of the physical containment and control technologies enumerated in 40 CFR part 725.422 for "any facility in which the microorganism is to be used." It is unlikely that off-site transportation of live genetically modified microorganisms could be accomplished under the physical containment and control restrictions required to qualify for the Tier I exemption.

Certain intergeneric microorganisms in R&D field testing are also exempt. Testing on ten acres or less involving *Bradyrhizobium japonicum* and *Rhizobium meliloti* is exempt when certain exemption criteria specified by these rules are met.

Biofuels

The new chemicals regulated under TSCA by EPA include certain biofuels and certain microorganisms used in the production of biofuels. Some biofuels and synthetic fuels may be new chemicals, and thus, would be subject to Premanufacture Notice (PMN) reporting requirements, and as described above, there are analogous rules requiring MCAN submission for "new" microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc.) that are "intergeneric" genetically-engineered microorganisms.

Several prominent areas in the biofuels supply chain employ new chemicals and microorganisms. Success of many of the advanced fuel production technologies often depends on enhanced metabolic capabilities of microorganisms used in those technologies. Genetic engineering of microorganisms, using either traditional or synthetic biology approaches, may be necessary to achieve these enhancements. Since issuing the Biotechnology Rule, EPA has received numerous notifications, including for microorganisms critical in different parts of the fuel production processes for cellulosic ethanol manufacture. EPA has engaged companies regarding TSCA requirements for developing cellulosic ethanol and algal biofuels production and anticipates more notifications as these technologies mature in the next few years.

For More Information

For more detailed information on TSCA regulations concerning microbial products of biotechnology, refer to http://www.epa.gov/oppt/biotech.