Toxic Substances Control Act and Genetically Engineered Microorganisms

National Academies of Sciences, Engineering, and Medicine
Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System
4/18/2016 Public Meeting

Rebecca Edelstein, Ph.D.
Office of Chemical Safety and Pollution Prevention
Office of Pollution Prevention and Toxics
Chemical Control Division

Summary

- Introduction to the Toxic Substances Control Act (TSCA)
- 1986 Coordinated Framework and use of TSCA for biotechnology oversight
- Use of TSCA for oversight of New Microorganisms
  - TSCA uses
  - Exemptions
  - Types of submissions
  - Regulatory decisions
  - Emerging technologies

Toxic Substances Control Act (TSCA)

- Enacted in 1976
- Under TSCA, EPA has authority to regulate the manufacture, processing, use, distribution in commerce, and disposal of chemical substances and mixtures
- Covers chemical substances (industrial, environmental, or consumer products) not specifically excluded

Exclusions from TSCA

- Food, food additives
- Drugs
- Cosmetics
- Medical devices
- Pesticides (but not pesticide intermediates)
- Tobacco
- Nuclear material
- Firearms

TSCA Inventory of Chemical Substances

- an “existing” chemical substance is one that is listed on the TSCA Chemical Substance Inventory
- a “new” chemical substance is one that is not on the TSCA Inventory

Premanufacture Notification for New Chemical Substances

- TSCA section 5 established a 90-day process for EPA to screen new chemical substances before they are produced
- Notification is required for new chemical substances and is not triggered by a determination that risk is present
- During the review period, EPA determines whether to drop the substance from further consideration or to impose controls

Role of the Coordinated Framework and TSCA Biotech Oversight

- EPA issued a final Policy Statement in 1986 as part of the Federal "Coordinated Framework for the Regulation of Biotechnology"
- The Policy Statement outlines EPA oversight of "Intergeneric" microorganisms as new chemical substances under TSCA
- It formed the basis of TSCA biotechnology final regulations issued in 1997: Reporting Requirements and Review Processes for Microorganisms (40 CFR Part 725)

“New” Microorganisms Definition

New Microorganism = “intergeneric”

- Microorganisms formed by the deliberate combination of genetic material from organisms classified in different taxonomic genera
  - naturally occurring microorganisms – implicitly listed on the TSCA inventory - ***not new***
  - those formed by the introduction of genetic material from organisms within the same genus (intrageneric) - ***not new***
  - those containing only well-characterized, non-coding regulatory sequences – ***not new***
- Microorganisms constructed with synthetic genes that are not identical to DNA that would be derived from the same genus as the recipient

Typical TSCA Uses of Genetically Engineered Microorganisms

- Production of industrial enzymes and other chemicals
- Biosensors
- Production of biofuels
- Breakdown of chemical pollutants in the environment
- Agricultural uses (other than pesticides)

Exemptions from Full Reporting Requirements

- **Tier I Exemption**
  - Certain eligible recipient microorganisms
  - Criteria for the introduced genetic material
  - Specific containment & inactivation criteria
  - Certification of eligibility must be submitted to EPA at least 10 days before manufacture
- **Tier II Exemption**
  - Same criteria for recipient microorganism and introduced genetic material as for Tier I exemption
  - 45-day EPA review period to determine whether adequate physical containment and control technologies used and other criteria met
- **Research and Development Exemption**
  - Must meet specific criteria

TSCA Submissions for Intergeneric Microorganisms – Reporting Mechanisms

Microbial Commercial Activity Notice (MCAN)

- Any manufacturer (which includes importers) or processor must file a MCAN at least 90 days prior to initiating manufacture (unless eligible for an exemption)

TSCA Experimental Release Application (TERA)

- Persons who wish to introduce a new microorganism into the environment, for commercial research and development activity, must submit a TERA 60 days prior to initiation of the field test (similar to an abbreviated MCAN submission)

Premanufacture Notice (PMN)

- Manufacturer may also be required to submit a PMN if a new chemical substance is produced by the microorganism intended for a non-exempt use

Data and Information Considered During MCAN/TERA Review

- *Points to Consider* Guidance Document
  - Taxonomic description of the recipient and donor organisms
  - Detailed construction of the submission microorganism
  - Human health effects information
  - Environmental effects information on submission microorganism
  - By-products, production volume, and use information
  - Worker exposure and environmental release/containment
  - Environmental release protocols
  - Expected survival/dispersion (i.e., environmental exposures)
  - Emergency/contingency protocols

Possible Regulatory Decisions for MCANs

If EPA determines there is insufficient information and that manufacture or use of the microorganism may present unreasonable risk to human health or the environment:

- Up front testing
- TSCA section 5(e) Consent Order– binds manufacturer to certain conditions such as:
  - Limiting the site of manufacture or requiring particular manufacturing/processing methods
  - Development of information (e.g., monitoring, inactivation, toxicity studies)
- Significant New Use Rule (SNUR)– requires notice to EPA prior to new use

Possible Regulatory Decisions for MCANs

- If EPA determines there is no unreasonable risk to human health or the environment
  - Microorganism is dropped from further review
  - Manufacturer can begin commercial manufacture and submit Notice of Commencement
  - Microorganism is added to the TSCA Inventory and can be manufactured and used with no restrictions

Emerging Technologies

- EPA has issued “Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms”
- Guidance provides comprehensive list of data and information that may be useful for a variety of TSCA biotechnology submissions
- Guidance also provides help in organizing and presenting relevant data and information
- “Points to Consider” were last updated in 1997; EPA is now beginning update for two categories of information not previously considered: algae production and modern modes of advanced genetic engineering
- EPA held workshop to solicit public input for “Points to Consider” update on 9/30/2015

  https://projects.erg.com/conferences/oppt/workshophome.htm
- Plan to update “Points to Consider” and develop a “Considerations for Biotechnology Algae” document

Office of Chemical Safety and Pollution Prevention

Overview of Biotechnology under TSCA

https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/overview-biotechnology-under-tsca

Microbial Products of Biotechnology; Final Regulation Under the Toxic Substances Control Act; Final Rule

40 CFR Parts 700, 720, 721, 723, and 725 (62 FR 17910; April 11, 1997)

https://www.gpo.gov/fdsys/pkg/FR-1997-04-11/pdf/97-8669.pdf

Points to Consider in the Preparation of TSCA Biotechnology Submissions for Microorganisms

https://www.epa.gov/sites/production/files/2015-08/documents/biotech_points_to_consider.pdf

FIFRA resources

Regulation of Future Products of Biotechnology Under FIFRA and FFDCA

National Academies of Sciences, Engineering, and Medicine
Future Biotechnology Products and Opportunities to Enhance Capabilities of the Biotechnology Regulatory System
4/18/2016 Public Meeting

Chris A. Wozniak, Ph.D.
U.S. Environmental Protection Agency,
Office of Pesticide Programs
Biopesticides and Pollution Prevention Division
April 18, 2016

EPA's Biotechnology Program Decisions

- Are protective of man and the environment
- Use sound science
- Use independent scientific experts, e.g. FIFRA Scientific Advisory Panel (SAP)
- Involve collaboration with regulatory partners
- Are consistent, fair, and transparent

U.S. Pesticide Laws

Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

- Distribution, use and sale of pesticides: registration, emergency exemption, state registration for special local need.
- Re-evaluation of older pesticides.
- Field testing and distribution of experimental pesticides.

U.S. Pesticide Laws (cont.)

Federal Food, Drug, and Cosmetic Act (FFDCA)

- Establish tolerances (maximum residue levels) for pesticides on food and feed.
- Tolerances apply to both domestic and imported foods.

Registration of Pesticides

FIFRA Standard - EPA may register a pesticide if, when used in accordance with widespread and commonly recognized practice, it generally will **not cause unreasonable adverse effects on human health or the environment.**

FFDCA Standard - EPA may establish a tolerance or tolerance exemption if there is **a reasonable certainty that no harm** will result from residues of the pesticide in food or feed.

Types of Biotech Pesticides Registered

- Microbial Pesticides
- Plant-Incorporated Protectants

Microbial Pesticides

- Includes microorganisms used as pesticides, e.g. bacteria, algae, fungi, viruses, bacteriophages; both naturally occurring and genetically engineered.

- Pesticidal modes of action can include competition, antibiosis, toxicity, pathogenicity to pests, parasitism, defense signaling, etc.

Genetically Modified Microbial Pesticides

- Small Scale Testing Notification Requirement
- Is an Experimental Use Permit needed for testing under 10 acres?
- 40 CFR Part 172.45 – Pesticidal properties have been imparted or enhanced by the introduction of genetic material that has been deliberately modified.

What is a Plant-Incorporated Protectant?

- A Plant-Incorporated Protectant (PIP) is a pesticidal substance, intended to be produced and used in a living plant or in the produce thereof, and the genetic material necessary for production of such pesticidal substance. Includes inerts contained in the plant or its produce.

Plant-Incorporated Protectants

- EPA oversees the pesticidal substance produced by plants (e.g. Bt Cry1Ab protein) and the genetic material necessary for its production (e.g. cry1Ab gene).

- PIPs that have been evaluated for commercial use include Bt crops and plant virus protected crops.

Herbicide Tolerant Plants

- EPA regulates the chemical herbicides used on herbicide tolerant plants

Considerations in Decision Making

- Molecular Characterization and Pesticidal Substance Expression Levels
- Human Health Assessment – Toxicity and Allergenicity
- Environmental Assessment – Non-Target Organism Effects, Environmental Fate, and Gene Flow
- Resistance Management
- Will future products require additional risk considerations?

Double Stranded RNAs

- dsRNA may be generated in a microbial system or synthetically
- Disease and pest resistance mechanisms
- May be used as a topical application or housed within a bait
- Can also be applied to herbicide resistant weeds to restore susceptibility

Gene Edited Traits

- Disease and Insect resistance through gene modification and silencing
- Defense signaling / induction
- Drought tolerance
- Algae for biofuels with altered metabolites
- Synthetic coding sequences

Useful Websites

- Biopesticides - Regulation and general information https://www.epa.gov/pesticides/biopesticides
- PIP Registrations - https://www.epa.gov/ingredients-used-pesticide-products/current-previously-registered-section-3-plant-incorporated
- RNAi technology as a pesticide - SAP report https://www.epa.gov/sites/production/files/2015-06/documents/012814minutes.pdf