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Don’t Be Caught Unaware: Regulatory Requirements Applicable to Microorganisms Released to the Environment

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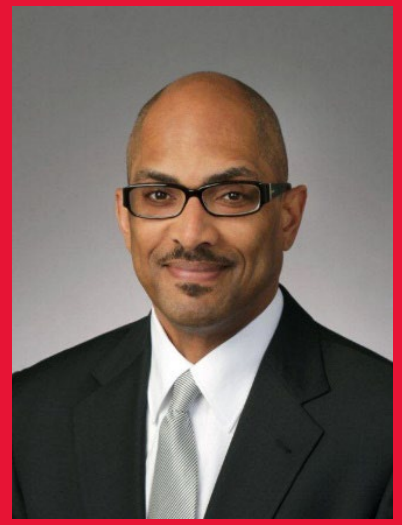

Background

Release of living organisms into the environment can be subject to regulation by either the U.S. Department of Agriculture (USDA), the Environmental Protection Agency (EPA), or both.

USDA and EPA can regulate such releases under the Plant Protection Act (PPA); the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Toxic Substances Control Act (TSCA), the Safe Drinking Water Act (SDWA), or various combinations of these statutes.

In addition to primary regulation under the PPA, FIFRA, TSCA, or SDWA, other subsidiary statutes and regulatory requirements may come into play.

Background

In this talk, I will subdivide purposeful release of organisms into the environment into (1) industrial and/or bioremediation uses; and (2) agricultural uses;

FIFRA applies to agricultural uses, to agricultural pest and weed control uses, and to pest and weed control uses;

The PPA applies to any release into the environment of a microorganism that may be a plant pest; and

TSCA applies to non-FIFRA uses of certain microorganisms.

Background

Polling Questions:

1. I'm a researcher and I've found a new strain of a naturally occurring microorganism that degrades an organic contaminant, is the newly found strain subject to TSCA?

a) Yes
b) No

2. I'm a researcher and I've taken a contaminant degradation trait from one strain of a microorganism and genetically engineered it into a second strain of the same species, is the newly genetically engineered strain of the microorganism subject to TSCA?

a) Yes
b) No

Background

Polling Questions:

3. I'm a researcher and a colleague has discovered a naturally occurring microorganism in Asia that degrades an organic contaminant and I want to import the microorganism to the U.S., is the newly found microorganism subject to TSCA?

a) Yes
b) No

4. I'm a researcher and a colleague has discovered a naturally occurring microorganism in Asia that degrades an organic contaminant and I want to import the microorganism to the U.S., is the newly found microorganism subject to regulation by USDA?

a) Yes
b) No

Coordinated Framework Regulatory Context

USDA	EPA	FDA

▪ Environmental Releases
  ▪ Field testing
  ▪ Permits
▪ Notifications
▪ Determination of regulated status
	▪ Plant Incorporated Protectants (PIPs)
	▪ GE Microbes (agricultural and industrial)
		▪ Food and Feed safety consultation (voluntary)

Scope	**Scope**	**Scope**
All Potential Plant Pests	GE organisms	Food, Feed, Pharmaceuticals
Statutory Authority	**Statutory Authority**	**Statutory Authority**
Plant Protection Act (PPA) National Environmental Policy Act (NEPA)	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Federal Food, Drug, and Cosmetic Act (FFDCA) Endangered Species Act (ESA) Toxic Substances Control Act (TSCA)	Federal Food, Drug, and Cosmetic Act (FFDCA) Endangered Species Act (ESA)

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US Coordinated Framework For Biotechnology

USDA

Mandate:

Evaluation of Plant Pest Potential

Data Evaluated:
- Gene/Protein Safety
- Compositional equivalence
- Ag/Pheno characterization
- Environmental Safety/NTO

Review Focus : Two main questions

Does the Product pose a significant Plant Pest Risk? (PPA)

NO → Does the product have the potential for a significant environmental impact? (NEPA)

YES → Determination of Regulated Status

NO → **Environmental Assessment (EA)**

YES → **Environmental Impact Statement (EIS)**

Finding of No Significant Impact (FONSI)

Public Comment (≥ 30 Days)

→ Determination of Non-Regulated Status

EPA

Mandate:

Evaluation of Human Health and Environmental Risks

Data Evaluated:
- Gene/Protein Safety
- Allergenicity/Toxicity Non-Target Organism Effects (NTO)
- Environmental Effects

Review Focus : Four Federal Statutes

Does dietary exposure to the Food/Feed derived from the product pose a health risk? (FFDCA)

→ **Conclusion:** There is a reasonable certainty of no harm from

Does the pesticide safety pose an unreasonable risk to the environment or human/animal safety? (FIFRA)

→ **Conclusion:** The pesticide safety does not pose a risk to the environment or human or animal safety

FDA

Mandate:

Evaluation of Food and Feed Safety

Data Evaluated:
- Gene/Protein Safety
- Allergenicity/Toxicity
- Compositional equivalence
- Consumption

Review Focus (FFDCA):
- Allergenicity/Toxicity
- Nutritional Composition

Conclusion:
The new food/feed is as safe as its non-modified counterparts

YES → Consultation Completed

NO → Additional Consultation with FDA → Consultation Completed

TSCA -- The Toxic Substances Control Act

- TSCA regulates the manufacture (including importation) and use of chemical substances in U.S. commerce
- A chemical substance in commerce in the United States must be on the “TSCA Inventory”
- Microorganisms may be regulated under TSCA as chemical substances
- Naturally occurring microorganisms that are not intergeneric are implicitly included on the TSCA Inventory

TSCA

"New" microorganisms that are not included on the TSCA Inventory include:

"Intergeneric" microorganisms (including bacteria, fungi, algae, viruses, protozoa, etc.) formed by combining genetic material from organisms in different genera

- **intergeneric microorganism:** a microorganism that is formed by the deliberate combination of genetic material originally isolated from an organism(s) in a different taxonomic genera.
  - Does *not* include: a microorganism that contains introduced genetic material consisting of only well-characterized, non-coding regulatory regions from another genus.

TSCA

Intergeneric microorganisms: "a microorganism that is formed by the deliberate combination of genetic material originally isolated from organisms of different taxonomic genera."

- Note: wrt chemically synthesized genes, if the genetic sequence of a synthetic gene is identical to a sequence known to occur in an organism in the same genus, the resulting microorganism is considered *intra*generic. Conversely, if the sequence of a synthetic gene is different than, or is not known to be identical to an existing sequence in the genus of the recipient microorganism, the resulting microorganism is considered to be intergeneric.

TSCA - Intergeneric microorganisms

What requirements are applicable to "new" microorganisms (1):

MCAN – Microbial Commercial Activity Notice

- ❑ Submitter identification;
- ❑ Microorganism identity information, including a description of the recipient and new microorganisms, genetic construction, and phenotypic and ecological characteristics;
- ❑ Byproducts of manufacture, processing, use, and disposal of the new microorganism;

TSCA - Intergeneric microorganisms:

What requirements are applicable to "new" microorganisms (2):

MCAN – Microbial Commercial Activity Notice

- ❑ Total production volume;
- ❑ Use information;
- ❑ Description of worker exposures and environmental releases; and
- ❑ Existing health and environmental effects data.

Note that while EPA's regulations do not require that companies generate and submit kill curve and inactivation data, this information should be included in the MCAN submission as EPA typically requests it during its review.

TSCA - Intergeneric microorganisms:

Potential Regulatory Actions (MCAN):

- Unrestricted use in commerce permitted.
- "Negotiation" of a consent order that limits permitted uses and imposes conditions of use.
  - Could include workplace protection, testing, waste disposal, and restrictions on releases from the facility.
- Proposed "significant new use rule" (SNUR) that imposes such conditions generally.
  - (a consent order only binds the company that negotiates and signs the order with EPA)

TSCA – Naturally occurring microorganisms

Even if a microorganism is naturally occurring, it could be subject to a SNUR

Significant New Use Rules

Burkholderia Cepacia Complex; Significant New Use Rule, 68 Fed. Reg. 35,315 (June 13, 2003) (codified at 40 C.F.R. § 721.1075) (for *Burkholderia cepacia* complex (Bcc), a group of naturally occurring microorganisms, for any use other than research and development in the degradation of chemicals via injection into subsurface groundwater).

Regulation of Pesticides Under FIFRA

Pesticides

In the United States, pesticides are regulated by EPA under authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)

7 U.S.C. § 136-136y

Regulation of Pesticides Under FIFRA

"Pesticides"

FIFRA § 2(u) defines "pesticides" as:

(1) Any substance or mixture of substances *intended* for preventing, destroying, repelling, or mitigating any pest

and

(2) Any substance or mixture of substances *intended* for use as a plant regulator, defoliant, or desiccant

U.S. Regulation of Pesticides - EPA

Plant Regulators

- "… any substance or mixture of substances intended, *through physiological action*, for *accelerating or retarding the rate of growth or rate of maturation,* or for *otherwise altering the behavior of plants or the produce thereof* …"
- excluding:
  - plant nutrients/nutritional chemicals
  - trace elements
  - plant inoculants
  - soil amendments
  - vitamin-hormone horticultural products

7 U.S.C. 136(v)

Regulation of Microbes Under FIFRA

EPA regulates microbes that are intended for pesticidal use under FIFRA.

If a microorganism is regulated under FIFRA, it is not subject to regulation under TSCA

Microorganisms regulated under FIFRA are intended to "prevent, destroy, repel, or mitigate" pests or weeds; or to effectuate a plant regulator function.

Regulation of Plants Under FIFRA

EPA also regulates plants that are intended for pesticidal use under FIFRA.

Typically, genetically engineered plants that are intended to "prevent, destroy, repel, or mitigate" specific pests in an environmentally cabined manner.

Regulation of Plants Under FIFRA

But, what if a plant is genetically engineered to enhance bioremediation properties?

Could that be a “plant regulator” use subject to regulation under FIFRA?

U.S. Regulation of Pesticides - EPA

Plant Regulators

- "… any substance or mixture of substances intended, *through physiological action*, for *accelerating or retarding the rate of growth or rate of maturation,* or for *otherwise altering the behavior of plants or the produce thereof* …"
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7 U.S.C. 136(v)

USDA Regulation of Plant Pests

USDA regulates microbes that are, or may be, plant pests under regulations at 7 C.F.R. Parts 330 and 340.

USDA regulates microbes generally under Part 330 and regulates GE microbes under Part 340.

But, sometimes, the distinction is not so clear.

USDA Regulation of Plant Pests

The Plant Protection Act defines "plant pest" as:

[A]ny living stage of any of the following that can directly or indirectly injure, cause damage to, or cause disease in any plant or plant product:

(A) A protozoan.
(B) A nonhuman animal.
(C) A parasitic plant.
(D) A bacterium.
(E) A fungus.
(F) A virus or viroid.
(G) An infectious agent or other pathogen.

USDA Regulation of Microbes

USDA regulates microbes that are, or may be, plant pests under regulations at 7 C.F.R. Parts 330 and 340.

USDA regulates microbes generally under Part 330 and regulates GE microbes under Part 340.

But, sometimes, the distinction is not so clear.

USDA Regulation of GE Microbes

7 C.F.R. Part 330:

"Federal Plant Pest Regulations; General; Plant Pests, Biological Control Organisms, and Associated Articles; Garbage"

Plant Pest and Quarantine

7 C.F.R. Part 340:

"Movement of Organisms Modified or Produced Through Genetic Engineering"

Biotechnology Regulatory Service

USDA Part 340 Final Rule

Under the revised Part 340, product developers are required to obtain a permit for GE organisms if (1) the plant and trait mechanism of action (plant-trait-MOA) combination has not been previously evaluated by APHIS; (2) it is a plant pest; (3) it is a non-plant organism that has received DNA from a plant pest; (4) it is a microorganism that can control plant pests or is a parasite that can control invertebrate plant pests, and could be a plant pest risk; or (5) is a plant that produces a pharmaceutical or industrial use product.

Other Environmental Statutes

- A remediation project that involves the subsurface emplacement of fluids, including microbes and nutrients, through injection wells is regulated under the Federal Safe Drinking Water Act (SDWA) Underground Injection Control (UIC) Program.
- Groundwater injection wells are regulated as Class V wells under the Federal UIC program.
- In most cases, Class V wells are “authorized by rule” which means that the wells may be operated without a permit provided the owner/operator takes the following actions:
  - Submits inventory information to their permitting authority and verifies that it is authorized to inject;
  - Operates the well in a manner that does not endanger underground sources of drinking water; and,
  - Properly closes the wells then they no longer need to be used.
- EPA has granted primary enforcement authority to 31 states to operate the UIC program for multiple well classes, including Class V wells.
  - State programs can be stricter than the Federal program.

Other Environmental Statutes

- But, UIC authorization does not relieve an owner/operator of responsibility for releases outside the scope of the UIC authorization.
- During a 2020 injection of remedial amendments in Pennsylvania, the environmental consultant noticed that there did not seem to be enough back pressure during injection at the fourth of eight planned injection points.
  - The remedial amendments included a vegetable oil biostimulant and a proprietary abiotic reductant.
  - The consultant inspected the scene and discovered a milky white discharge in a nearby creek, indicating that the remedial amendments were discharging to the creek. The consultant ceased injection.
  - The release triggered spill reporting to the National Response Center under the federal Clean Water Act and to the Pennsylvania Department of Environmental Protection under state law.

Polling Questions – Part 2

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a) Yes
b) No

2. I'm a researcher and I've taken a contaminant degradation trait from one strain of a microorganism and genetically engineered it into a second strain of the same species of microorganism, is the newly genetically engineered strain subject to TSCA?

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Polling Questions – Part 2

3. I'm a researcher and a colleague has discovered a naturally occurring microorganism in Asia that degrades an organic contaminant and I want to import the microorganism to the U.S., is the newly found microorganism subject to TSCA?

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4. I'm a researcher and a colleague has discovered a naturally occurring microorganism in Asia that degrades an organic contaminant and I want to import the microorganism to the U.S., is the newly found microorganism subject to regulation by USDA?

a) Yes
b) No

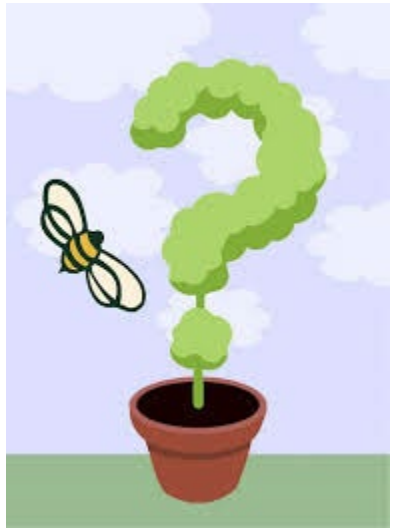
Polling Questions – Part 2

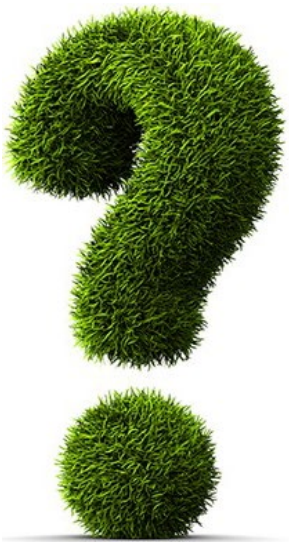
5. I'm a researcher and I've genetically engineered Arabidopsis to take up an environmental contaminant from soil and sequester it in plant tissues, is the GE Arabidopsis subject to:

a) TSCA
b) FIFRA
c) The PPA
d) a and b
e) a and c
f) b and c

Wiley Resources

- https://www.wiley.law/practices-Environment
- https://www.wiley.law/alert-What-Every-Company-Needs-to-Know-About-TSCA-Reviews-for-Industrial-Biotechnology-Products





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