August 29, 2024

Mrs. Chessa Huff-Woodard
USDA Animal and Plant Health Inspection Service
Biotechnology Regulatory Services
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via regulations.gov

RE: Request for Information: Exploring Pathways to Commercialization for Modified Microbes, Docket No. APHIS-2024-0002-0001

Dear Mrs. Chessa Huff-Woodard,

The Breakthrough Institute (BTI) appreciates the opportunity to comment on the APHIS BRS Request for Information: Exploring Pathways to Commercialization for Modified Microbes, Docket No. APHIS-2024-0002-0001. BTI is an independent 501(c)(3) global research center that identifies and promotes technological solutions to environmental and human development challenges. BTI's Food and Agriculture program researches and advocates for policies and strategies to improve productivity growth and reduce the carbon footprint and other environmental impacts of agriculture.

Modified microbes have great potential to improve agricultural production, for example by improving crop drought tolerance and therefore productivity under increasing water scarcity, or by improving nitrogen fixation and therefore decreasing fertilizer application and associated nitrous oxide emissions. Regulation of modified microbes must support commercialization and realization of benefits like these and others, while minimizing potential plant pest risk. Regulation must also support the ability of small and medium developers and academic institutions to submit regulatory applications for modified microbes. Below we provide our perspective on regulations that could accomplish these goals.

Respectfully submitted,
Emma Kovak, PhD
On behalf of the Breakthrough Institute

Responses to APHIS questions in RFI

1. Describe new or emerging categories of biotechnology products that are relevant to the development and use of modified microorganisms. To assess new and emerging technologies with modified microbes, what expertise and resources are needed in the government to evaluate the overall plant pest risk of modified microbes?

In order to assess the risks of adding modified microbes to agricultural fields, agencies need more information on the potential for unintentional spread via runoff from fields. If a modified microbe has a plausible pathway for plant pest risk, then understanding the range of

environments that will be exposed to the modified microbe is important for defining the potential risk because a novel trait could have different impacts in different environments. However, if the unmodified microbe is not novel in an agricultural environment, or if the unmodified microbe is novel but does not pose plant pest risk, and the modified trait has no plausible pathway for plant pest risk, then information about microbial spread is unnecessary.

The government could support a body of information on microbial spread in several ways.

First, since developers often conduct lab and field studies to measure the ability of the microbes they develop to spread in the environment, the government could find a way to incentivize companies to make the studies public, and ideally create a public database for these studies. Such data sharing could decrease the barrier to entry for developers by reducing the tests they must conduct on new products, and could save regulators time because they wouldn't need to review new evidence on microbial spread in the environment with every product application. A database with this information could also support data sharing between agencies, further decreasing regulatory redundancy.

Second, the government could increase funding for the Biotechnology Risk Assessment Research Grants (BRAG) program. Funding from the program could support further research on the ability of different microbes to spread from agricultural fields, and make the results public to benefit both developers and agencies. BRS could also engage with precompetitive research efforts through FFAR, ARS, NIFA, and NSF to raise awareness around BRS concerns and needs.

2. Describe areas where the clarity and/or efficiency of regulations governing modified microorganisms could be improved (e.g., definitions that need to be provided or revised, barriers to obtaining the data necessary to achieve commercialization).

Currently, the SECURE rule provides extremely limited exemptions for modified microbes (e.g. disarmed Agrobacterium), which is not only unnecessarily restrictive but is also not sustainable given current agency capacity or any reasonable expectation for future expanded agency capacity. Below we discuss additional exemptions that USDA could provide for other low-risk modified microbes in addition to disarmed Agrobacterium. USDA has seen a substantial increase in applications for review of genetically engineered plants under the SECURE rule, and BRS is struggling to keep up with the volume of applications while meeting set timelines for completion of review.[1]

Another factor that will contribute to agency overwhelm is the lack of a decision tree or clear guidance between and within agencies as to which will regulate a given modified microbe. It is unsustainable with regards to agency capacity to expect all applicants to ask for consultation

[1] Emma Kovak and Emily Bass. 2024. Can Regulators Keep Up With Biotech Innovation? The Breakthrough Institute. https://thebreakthrough.org/issues/food-agriculture-environment/can-regulators-keep-up-with-biotech-innovation

with the agency before submitting an application. Rather, USDA should provide a clear list of exemptions and a description of what types of modified microbes the agency has oversight over that allows developers to identify the regulatory path their product will take.

In addition, the agency should allow modified microbes to go through the confirmation process, which is currently only available for modified plants under SECURE. Even for exempted microbial products, developers should have the option of going through a process to confirm the exemption, which provides more certainty before commercialization and may be helpful in applications for commercialization in other countries.

3. Describe key elements of a regulatory framework that would enable a scientifically sound assessment of a modified microorganism's plant pest risk, in order to inform regulatory decision-making by APHIS.

a. What criteria, data, and information should be considered when assessing a modified microoganism's plant pest risk?

As a NASEM panel of experts suggests in a 2016 report titled "Genetically Engineered Crops: Experiences and Prospects,"[2] risk assessment should be based on the characteristics of the modified organism and the environment into which it will be introduced. Though the report focuses on plants, these features of risk assessment are widely applicable, including to other genetically engineered organisms.

Based on the canonical elements of risk assessment — hazard and exposure — the report suggests three elements to guide risk assessment of new genetically engineered crops: novelty, potential hazard, and exposure. According to the expert authors, premarket screening should focus on plants that express traits that are new to crop production and that pose potential harm. Traits that are new to crop production or crop species can pose a novel exposure, but in order to justify imposing restrictions there must also be a plausible potential for harm. Regulators must also take into account the extent of uncertainty regarding potential harm.

When assessing a modified microbe's plant pest risk, APHIS should consider whether a microbe commonly occurs in agricultural fields. If the developer originally isolated the microbe from agricultural soils or plant tissue before modifying it, or if there is published sequencing data or other evidence that the microbe occurs in agricultural soils or on crops, then the only new aspect of the product to an agricultural context is the modification. If a microbe commonly occurs in agricultural soils or on crops, then it in some sense has a history of safe use. In addition, if the unmodified microbe is part of an existing commercialized microbial treatment for agricultural crops or soils that has not posed any problems the agency is aware of, then the unmodified microbe has a history of safe use as an agricultural input. This allows APHIS to conduct a comparative risk

[2] National Academies of Sciences, Engineering, and Medicine. 2016. Genetically Engineered Crops: Experiences and Prospects. Washington, DC: The National Academies Press. https://doi.org/10.17226/23395

assessment to determine whether the modified microbe poses any plant pest risk beyond that of the unmodified microbe.

Compared to modified microbes where the unmodified microbe commonly occurs in agricultural soils, introduction of a microbe that does not commonly live in agricultural soils or on crops has substantially more potential unknown impacts due to its biology in addition to the modification.

APHIS should also consider existing evidence showing whether the unmodified microbe poses a plant pest risk.

b. What should APHIS consider when determining whether modification of a biocontrol organism could result in it posing a plant pest risk? Provide scientific evidence to support which types of biocontrol organisms and methods could or could not pose a plant pest risk.

APHIS should not perform premarket screening for biocontrol microbes, because this activity would duplicate EPA's regulation of microbial pesticides, which the agency regulates along with two other classes of biopesticides. USDA would regulate biocontrol microbes for plant pest risk, but EPA's oversight also includes examining the impacts of biopesticides on plants.

5. Should APHIS consider risk-based exemptions for certain types of microorganisms, or for certain modifications in microorganisms? If so, please provide examples of the types of modified microorganisms that should be exempt from regulation and provide scientific evidence to support which modifications and types of microorganisms should or should not be exempt.

APHIS should exempt modified microbes if the unmodified microbe commonly occurs in agricultural soils or on crop plants, and the modified trait is low risk. This should include modified microbes where the unmodified microbe commonly occurs in agricultural soils or on crop plants and there is published data showing the microbe is a plant pest, as long as the modification has no plausible pathway to increase plant pest risk.

APHIS should also exempt modified microbes if the unmodified microbe does not commonly occur in agricultural soils or on crop plants but there is evidence showing the unmodified microbe is not a plant pest, and the modified trait is low risk. Conversely, APHIS should not exempt modified microbes if the unmodified microbe does not commonly occur in agricultural soils or on crop plants and there is a plausible pathway to increased plant pest risk.

Even for exempted products, developers should have the option of going through a process to confirm the exemption.

Low-risk traits should include:

- Barcoding traits, because they are specifically designed to not make a protein or other product or contribute to any other phenotype.

- Traits that increase nitrogen fixation activity or add a nitrogen fixation pathway, because nitrogen fixation is not a new trait in agricultural crops, and many nitrogen fixing microbes live in soils with both legumes and non-legumes, both in association with the plant as well as free living. In addition to the low potential for risk, the benefits of these products helping to reduce fertilizer application and associated negative environmental impacts like soil nitrous oxide emissions and eutrophication of water bodies are too great to slow these products' commercialization.
- Traits that increase or decrease production of any metabolite that the microbe already makes if there is no plausible pathway to increased plant pest risk, because the metabolite is known and does not constitute a novel exposure.