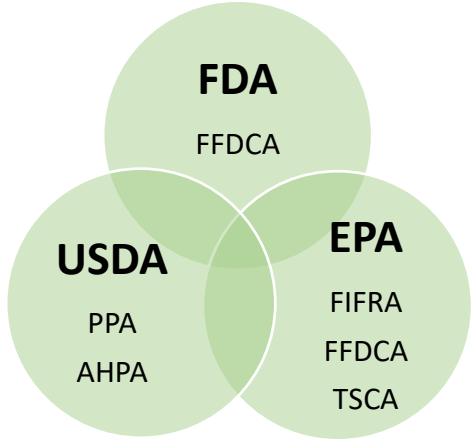
Final Rule

Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived from Newer Technologies

US regulation of modern biotechnology products

- EPA, USDA, and FDA regulate biotechnology products under the "Coordinated Framework for Regulation of Biotechnology." (1986 and 2017)

- Agencies regulate products of biotechnology using their existing statutes.
  - FDA determines whether foods/feed grown from crops modified by modern biotechnology are as safe as their conventional counterparts
  - USDA is responsible for protecting agriculture from pests and disease
  - EPA's OPP regulates the use of pesticides and whether they are safe for humans and the environment.



- One product may be regulated by multiple Agencies.

- The protection goals of each Agency determine how the product is evaluated and regulated.

EPA regulates pesticides produced and used in plants

Plant-incorporated protectants (PIPs)

- PIPs are comprised of the pesticidal substance produced and used in the living plant and the genetic material necessary for its production.

- Also included in the regulatory definition are any inert ingredients present in the plant used to confirm the presence of the pesticidal substance, e.g., herbicide resistance trait.

PIPs are subject to the same statutes as all other pesticides

- Under FIFRA: EPA evaluates pesticides including PIPs for their effects on the environment and human health and regulates their development, sale, distribution, and use.

- Under FFDCA: EPA evaluates PIPs that are proposed for use in food or feed. In its assessment the Agency considers all anticipated dietary exposures, residential and other outdoor uses.

Exemptions for genetically engineered PIPs

EPA's final rule allows for certain PIPs created through genetic engineering to be exempt in cases where those PIPs:

1) Pose no greater risk than PIPs that EPA has already concluded meet safety requirements, and
2) could have otherwise been created through conventional breeding.

Determine the eligibility for exemption:

1) Request EPA confirmation that their PIP meets the criteria for exemption, and/or
2) a developer may submit a self-determination letter.

Only developers of "loss-of-function PIPs" are currently allowed to self-determine.

This rulemaking updates regulations based on advances in biotechnology

- Scientific advances now provide technologies to modify the genome such that plants modified using biotechnology can be indistinguishable from conventionally bred plants.

- This rule is an effort to implement the policy goals articulated by multiple administrations to improve, clarify, and streamline regulations of biotechnology, including Executive Order 14081 on “Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy” (87 FR 77901; December 20, 2022).

- EPA anticipates that today’s exemptions will benefit the public by ensuring that human health and the environment are adequately protected, while also reducing the regulatory burden.

- These exemptions may also result in commercialization of new pest control options for farmers, particularly in minor crops, and increase the diversity of options for pest and disease management, which could provide environmental benefits.

Key features of the Final Rule

1. Creates an exemption for the category of **"PIPs created through genetic engineering from a sexually compatible plant"** at 40 CFR 174.26.
2. Creates an exemption for the category of **"loss-of-function PIPs"** at 40 CFR 174.27.
3. Establishes Subpart E of 40 CFR 174 to describe an **exemption eligibility determination process** for PIPs in this rulemaking and lists exemption specific information required for submission.
4. Issues **recordkeeping requirements** for PIPs in this rulemaking.

In addition, the Final Rule does the following:

5. Clarifies general qualifications for exemption at 40 CFR 174.21.
6. Clarifies relationship between the existing exemptions for PIPs from sexually compatible plants (40 CFR 174.25) and the newly issued exemption for "PIPs created through genetic engineering from a sexually compatible plant" (40 CFR 174.26).
7. Allows the existing inert ingredient exemption at 40 CFR 174.705 to include genetic engineering.

1. Exemption for “PIPs created through genetic engineering from a sexually compatible plant” 40 CFR 174.26

- **Insert a “native gene”**
  Allows for:
  - Insertion of a native gene to produce a substance identical in sequence to the pesticidal substance identified in the source plant.
  - The regulatory regions inserted as part of the native gene must be identical in nucleic acid sequence.

- **Modify an existing gene to create a “native allele”**
  Allows for:
  - Modifications of the existing native gene to match specific sequence(s) in a native allele of that gene. Does not require the entire gene to be modified.
  - Must use a single source plant as a template.

- **Expression profile**
  - It is not required that all regulatory regions from a native gene be inserted, but those that are inserted must meet the identical sequence criterion, which ensures that the expression profile of the genetically engineered PIP is equivalent to what is found in the sexually compatible source plant.
  - In addition, for PIPs in plants used for food, the levels of the active ingredient cannot be present at levels that are injurious or deleterious to human health (40 CFR 174.541(b)).

1. Exemption for “PIPs created through genetic engineering from a sexually compatible plant” 40 CFR 174.26

- New definitions such as “native genes” and “native alleles” limit the pesticidal substances to those characteristic of plants that are sexually compatible with the recipient plant.

- Specifically excludes transgenes that could be moved between sexually compatible plants through conventional breeding.
  - Example: A bacterial endotoxin from *B. thuringiensis* that was engineered into plant “A” (source plant) would not qualify as a native gene to be used in plant “B” (recipient plant) as *B. thuringiensis* and plant “B” are not sexually compatible.

- By limiting the pesticidal substances in this way, EPA can rely on the history of safe use associated with conventional breeding to conclude negligible risk of novel exposures or hazards.

2. Exemption for “Loss-of-function PIPs” 40 CFR 174.27

- “Loss-of-function PIPs” are characterized by a modification that leads to the reduction or elimination of the activity of that gene, which then results in a pesticidal trait (e.g., the inactivation of a gene coding for a plant receptor confers disease resistance).

- There must be a direct relationship between the loss of function of the native gene and the pesticidal effect, i.e., it is not a “loss-of-function PIP” if the loss of a native allele affects a second gene, which then produces a pesticidal substance.

- EPA regulates the modified genetic material that confers the pesticidal effect as the pesticidal substance and active ingredient.

- The loss-of-function PIP does not need to have been previously identified in a sexually compatible plant and there are no sequence specific requirements. The loss-of-function PIP exemption is based on function.

Additional information regarding the exemptions

- Multiple PIPs within a single plant
  - The exemptions at 40 CFR 174.26 and 40 CFR 174.27 do not limit the number of PIPs that can be created in a single recipient plant. Therefore, changes to multiple genes in a single recipient plant are allowed, so long as each resulting PIP individually meets the exemption criteria.
  - EPA considers multiple native gene insertions of the same gene to be one PIP, so the criterion related to safe expression levels in food plants (40 CFR 174.541(b)) would apply to the overall expression level from all inserted gene copies.
  - Similarly, a single loss-of-function PIP may require modification of several homologous genes of a native gene in a recipient plant.

- EPA acknowledges that the genetic variation that is observed in plants has the potential to be greater than what is captured in this rulemaking. Therefore, the Agency intends to revisit the question of capturing a broader range of genetic variation in the future.

- Any inert ingredients remaining in the final product must be listed as an approved inert ingredient in subpart X of part 174 (i.e., 40 CFR 174.705).

3. Eligibility determination process

- For a genetically engineered PIP to be eligible for exemption a developer must do at least one of the following:
  - Request for EPA confirmation.
  - Self-determination (currently only available for loss-of-function PIPs).

- Although “PIPs created through genetic engineering from a sexually compatible plant” are not currently eligible for the self-determination option, EPA intends to reconsider this in future rulemakings once the Agency and developers have gained experience.

- All submissions are required to be made electronically through EPA’s CDX portal.

3. Eligibility determination process

- **Information to be provided through the CDX portal**
  - Name and contact information .
  - Identity of recipient plant, unique identifier for the native gene from NCBI (NLM-NCBI), and trait type.
  - Any CBI claims must be substantiated.
  - A certification statement must be signed.
  - Non-CBI information from the portal will be used to create a public-facing list of all exempted genetically engineered PIPs.
- **Self-determination process**
  - Only developers of “loss-of-function PIPs” are currently allowed to self-determine.
  - Effective date of exemption: Once EPA notifies submitter.
    - EPA response is immediate due to electronic submission.

3. Eligibility determination process

- **<u>Requesting EPA confirmation</u>**
  - PRIA category M009.
  - If not already exempt through self-determination, the exemption is effective once EPA notifies submitter in writing.
  - Information required to be submitted:

Biology of plant	➢ Identity of the recipient plant, including genus and species ➢ Information to demonstrate that source and recipient plant are sexually compatible
Pesticidal trait	➢ Description of measures taken to ensure no engineering components are present in final product ➢ Description of measures taken to maximize likelihood modification is limited to intended modification
Molecular characterization	➢ Nucleic acid sequence comparison of PIP between recipient plant and comparators (+ amino acid sequence for proteinaceous PIPs)
History of safe use	➢ If substance is an allergen or mammalian toxin (e.g., solanine), describe how conventional breeding practices are being used to ensure that it does not exceed human dietary safety levels in the food plant ➢ If substance is from a wild relative, describe why the PIP is not anticipated to pose a hazard to humans or the environment

3. Eligibility determination process

Extension of exemption to other varieties of the same plant species

An exemption can be extended in two ways:

1. The exempted PIP is moved through conventional breeding into other varieties.
2. If the same submitter produces the identical substance through genetic engineering in another variety without any further modifications of the regulatory region (“PIPs created through genetic engineering from a sexually compatible plant”) or the same submitter targets the same native gene in a different plant variety to create a “loss-of-function PIP” through genetic engineering (“Loss-of-function PIPs”).

3. Eligibility determination process

Multiple PIPs within a single plant

- As previously stated, changes to multiple genes in a single recipient plant are allowed, so long as each resulting PIP individually meets the exemption criteria.

- The M009 PRIA fee for an EPA determination applies to each individual PIP, meaning that if one plant contains multiple unique PIPs, the M009 PRIA fee would apply multiple times.

- In the instance of modifying/inserting the same gene multiple times across the genome, the M009 fee is only applied once, as the application contains only one PIP.

4. Recordkeeping requirements

Developers of exempted genetically engineered PIPs must maintain for 5 years:

- Documentation of either the request for EPA confirmation or letter of self-determination, and
- Make documentation available to EPA upon request.

As is true for all PIPs, adverse effects reporting requirements apply.