including economic incentives—such as user fees or marketable permits—to encourage the desired behavior, or provide information that enables the public to make choices.

Executive Order 13563 also requires an agency ''to use the best available techniques to quantify anticipated present and future benefits and costs as accurately as possible.'' The Office of Information and Regulatory Affairs of OMB has emphasized that these techniques may include ''identifying changing future compliance costs that might result from technological innovation or anticipated behavioral changes.''

We are issuing this final priority and definition only on a reasoned determination that their benefits justify the costs. In choosing among alternative regulatory approaches, we selected the approach that maximizes net benefits. Based on the analysis that follows, the Department believes that this regulatory action is consistent with the principles in Executive Order 13563.

We also have determined that this regulatory action does not unduly interfere with State, local, and Tribal governments in the exercise of their governmental functions.

In accordance with these Executive orders, the Department has assessed the potential costs and benefits, both quantitative and qualitative, of this regulatory action. The potential costs are those resulting from statutory requirements and those we have determined as necessary for administering the Department's programs and activities.

Summary of Potential Costs and Benefits

The Department believes that the costs associated with the final priority and definition will be minimal, while the potential benefits are significant. The Department believes that this regulatory action does not impose significant costs on eligible entities. Participation in this program is voluntary, and the costs imposed on applicants by this regulatory action will be limited to paperwork burden related to preparing an application. The potential benefits of implementing the program will outweigh the costs incurred by applicants, and the costs of carrying out activities associated with the application will be paid for with program funds. For these reasons, we have determined that the costs of implementation will not be burdensome for eligible applicants, including small entities.

Paperwork Reduction Act of 1995

The final priority and definition contain information collection requirements that are approved by OMB under OMB control number 1820–0028; the final priority and definition do not affect the currently approved data collection.

Regulatory Flexibility Act Certification: The Secretary certifies that this final regulatory action will not have a significant economic impact on a substantial number of small entities. The U.S. Small Business Administration Size Standards define ''small entities'' as for-profit or nonprofit institutions with total annual revenue below $7,000,000 or, if they are institutions controlled by small governmental jurisdictions (that are comprised of cities, counties, towns, townships, villages, school districts, or special districts), with a population of less than 50,000.

The small entities that this regulatory action will affect are minority entities and Indian Tribes that may apply. We believe that the costs imposed on an applicant by the final priority and definition will be limited to paperwork burden related to preparing an application and that the benefits of the final priority and definition will outweigh any costs incurred by the applicant. We also believe that there are very few entities that can provide the type of technical assistance required under the final priority and definition. For these reasons, the final priority and definition will not impose a burden on a significant number of small entities.

Intergovernmental Review: This program is subject to Executive Order 12372 and the regulations in 34 CFR part 79. One of the objectives of the Executive order is to foster an intergovernmental partnership and a strengthened federalism. The Executive order relies on processes developed by State and local governments for coordination and review of proposed Federal financial assistance.

Accessible Format: On request to the program contact person listed under **FOR FURTHER INFORMATION CONTACT**, individuals with disabilities can obtain this document in an accessible format. The Department will provide the requestor with an accessible format that may include Rich Text Format (RTF) or text format (txt), a thumb drive, an MP3 file, braille, large print, audiotape, or compact disc, or other accessible format.

Electronic Access to This Document: The official version of this document is the document published in the **Federal Register**. You may access the official edition of the **Federal Register** and the Code of Federal Regulations at *www.govinfo.gov.* At this site you can view this document, as well as all other documents of this Department published in the **Federal Register**, in text or Portable Document Format (PDF). To use PDF you must have Adobe Acrobat Reader, which is available free at the site.

You may also access documents of the Department published in the **Federal Register** by using the article search feature at *www.federalregister.gov.* Specifically, through the advanced search feature at this site, you can limit your search to documents published by the Department.

Glenna Wright-Gallo,

Assistant Secretary for Special Education and Rehabilitative Services.

[FR Doc. 2023–11601 Filed 5–30–23; 8:45 am]

BILLING CODE 4000–01–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[EPA–HQ–OPP–2019–0508; FRL–7261–04–OCSPP]

RIN 2070–AK54

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

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: The Environmental Protection Agency (EPA) is exempting a class of plant-incorporated protectants (PIPs) that have been created using genetic engineering from certain registration requirements under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and from the requirements to establish a tolerance or tolerance exemption for residues of these substances on food or feed under the Federal Food, Drug, and Cosmetic Act (FFDCA). Specifically, EPA is finalizing its exemptions as described in its October 2020 proposal for PIPs now termed ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs,'' finalizing the process through which the Agency determines their eligibility for exemption, and finalizing the associated recordkeeping requirements. This set of exemptions reflects the biotechnological advances made since 2001, when EPA first exempted PIPs derived through conventional breeding and excluded from the exemptions those PIPs that are created through biotechnology. 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 for the regulated community. These exemptions may also result in increased research and development activities, 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.

DATES: This final rule is effective on July 31, 2023.

ADDRESSES: The docket for this action, identified under docket identification (ID) number EPA–HQ–OPP–2019–0508, is available at *https://www.regulations.gov.* Additional instructions on visiting the docket, along with more information about dockets generally, is available at *https://www.epa.gov/dockets.* For the latest status information on EPA/DC services and docket access, visit *https://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: Amanda Pierce, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460–0001; main telephone number: (202) 948–3693; email address: *BPPDFRNotices@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. Executive Summary

A. Does this action apply to me?

You may be potentially affected by this action if you are a developer or registrant of a PIP. This action also may affect any person or company who might petition the Agency for a tolerance or an exemption from the requirement of a tolerance for any residue of a PIP. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Pesticide and Other Agricultural Chemical Manufacturing (NAICS code 325320), *e.g.,* pesticide manufacturers or formulators of pesticide products, importers or any person or company who seeks to register a pesticide or to obtain a tolerance for a pesticide.
- Crop Production (NAICS code 111), *e.g.,* seed companies.
- Colleges, universities, and professional schools (NAICS code 611310), *e.g.,* establishments of higher learning which are engaged in development and marketing of PIPs.
- Research and Development in the Physical, Engineering, and Life Sciences (except Nanobiotechnology) (NAICS code 541714), *e.g.,* biotechnology research and development laboratories or services.

If you have any questions regarding the applicability of this action to a particular entity after reading the regulatory text, consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What action is the Agency taking?

This rule establishes exemptions under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. 136 *et seq.* and codified at 40 CFR 174.26 and 174.27 and for the residues of such PIPs under the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a and codified at 40 CFR 174.541 for certain PIPs that are created in plants using biotechnology. In this final rule, the term ''exemption'' is applied to actions under both of these statutes. (EPA notes that this action only exempts qualifying PIPs from regulation under FIFRA and the need to establish a tolerance for residues of qualifying PIPs under section 408(e) of the FFDCA; other statutory or regulatory requirements may still apply, *e.g.,* State, Tribal, or local requirements). This rule provides criteria and definitions that identify the two groups of PIPs that are exempted through this action, called ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs,'' and codifies the process through which the Agency determines their eligibility for exemption. The rule also codifies the recordkeeping requirements for exempted PIPs, and the preamble, along with the accompanying Response to Comments document (Ref. 1), addresses the public comments that the Agency received on the proposed rule (85 FR 64308; October 9, 2020; FRL–10014–10) (Ref. 2) during the public comment period. EPA's responses to those comments are summarized in Unit IV. and in the Response to Comments document (Ref. 1) that is available in docket for this action.

C. What is the Agency's authority for taking this action?

This action is being taken under the authority of FIFRA section 25 (7 U.S.C. 136w) and FFDCA section 408(e) (21 U.S.C. 346a(e)). FIFRA section 25(a)(1) authorizes EPA to issue regulations to carry out the provisions of FIFRA in accordance with certain procedures prescribed in that section. In addition, FIFRA section 25(b) allows EPA to promulgate regulations to exempt from the requirements of FIFRA any pesticide which the Administrator determines is ''of a character which is unnecessary to be subject to [FIFRA] in order to carry out the purposes of [FIFRA].'' FFDCA section 408(e) authorizes EPA to initiate actions to establish tolerances or exemptions for pesticide chemical residues that meet the safety standard. Section 408 of the FFDCA is focused on human risk. To make a safety finding under FFDCA to support a tolerance or exemption for pesticide residues on food, EPA considers, among other things: the toxicity of the pesticide and its metabolites and degradates, aggregate exposure to the pesticide in foods and from other sources of exposure, and any special risks posed to infants and children. The potential for pesticide exposure through food from food-producing animals that consume feed is part of the human health risk assessment used in EPA's FFDCA determinations. Risk to non-target organisms and risk associated with occupational exposure is evaluated under FIFRA. A more detailed discussion of EPA's statutory authority is available in Units III.A., III.B., and III.C. of the proposed rule (85 FR 64313–64314, October 9, 2020) (Ref. 2).

D. Why is EPA taking this action?

Recent advances in genetic engineering offer not only precise means by which genes coding for pesticidal substances can be inserted into a plant genome but also allow for modifications of genes that already exist within a plant. Due to the sophistication of these technologies, PIPs can now be created through genetic engineering that are virtually indistinguishable from those created through conventional breeding. These advances also allowed EPA to develop specific exemption criteria to circumscribe PIPs created through genetic engineering that pose no greater risk than the PIPs created through conventional breeding that have been exempt since 2001.

This rule is an effort to implement the policy goals articulated by multiple administrations to improve, clarify, and streamline regulations of biotechnology, beginning with the White House Office of Science and Technology Policy in a policy statement in 1986 on the ''Coordinated Framework for the Regulation of Biotechnology'' (51 FR 23302; June 26, 1986), the update to the Coordinated Framework in 2017 (Ref. 3), Executive Order 13874 (84 FR 27899, June 11, 2019) on ''Modernizing the

Regulatory Framework for Agricultural Biotechnology Products,'' and more recently, Executive Order 14801 (87 FR 56849, September 12, 2022) on ''Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy.''

E. What are the estimated incremental impacts?

EPA has evaluated the potential incremental impacts of the proposed exemptions in the document entitled ''Cost Analysis For the Final Rule Exempting Certain Plant-Incorporated Protectants (PIPs) from Registration'' (Ref. 4), which is available in the docket and is briefly summarized here.

1. Benefits

This rule reduces the regulatory hurdle (primarily cost) of getting certain PIPs to market. Accordingly, this rule is likely to encourage more research and development in this area of biotechnology and better enable firms of all sizes to engage in the development of these types of PIPs. Entities producing products designed for minor crops may not support markets large enough to warrant fixed registration costs. These entities may feel the most regulatory relief as a result of this rule.

Crop varieties modified for greater pest and disease resistance could increase the diversity of options for pest and disease management, which in turn, could provide environmental benefits and lower exposure for workers who apply pesticides. Growers may also benefit because they will have more tools available to combat pest pressures.

The rule is estimated to reduce overall registration costs (fees plus information and data requirement costs) to developers of ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs.'' On a per-product basis, the cost savings are estimated to range from $472,000–$886,000 using a 3% discount rate on future maintenance fees. A range of cost savings is provided because ''loss-of-function PIPs'' have fewer data requirements than ''PIPs created through genetic engineering from a sexually compatible plant'' and are not required to submit a request for EPA confirmation (thereby avoiding an M009 PRIA fee). Therefore, the savings to developers for ''loss-of-function PIPs'' is higher.

On an annual basis, the Agency estimates that anywhere from one to ten PIPs may be eligible for exemption. This upper and lower bound estimate is provided because, while the number of PIPs eligible for exemption is unknown, EPA has determined that it is likely to be greater than one. This is an increase from the estimate provided in the cost analysis for the proposed rule, which only included savings from one PIP. Accordingly, EPA estimates the annual savings of this rule to range from $472,000–$8,856,000 using a 3% discount rate on future maintenance fees (the lower bound represents one PIP per year and the upper bound represents ten PIPs per year will be eligible for exemption).

Of the entities likely to develop the types of PIPs this rule exempts, EPA currently estimates that approximately 80% are small entities. These cost savings would be realized as EPA approval of new active ingredients are sought. These exemptions are likely to remove a potential barrier to market entry for small entities because the monetary investment via Pesticide Registration Improvement Act (PRIA) fees and information and data requirement costs are substantially reduced from what would have been required under the registration process (in the absence of this rulemaking).

2. Costs

The costs of the rule includes costs imposed on developers and differences to societal welfare as a result of the rulemaking. The cost imposed on developers of PIPs include the costs to:

- Meet the requirements of the eligibility determination process per 40 CFR 174, subpart E;
- Maintain records related to the requirements of the eligibility determination for five years starting from the effective date of the exemption per 40 CFR 174.73; and
- Report any information regarding adverse effects on human health and the environment alleged to be caused by the PIP be reported to EPA per 40 CFR 174.71.

These costs are outlined in the cost analysis for the final rule. In consideration of the benefits and costs of the rule, the net effect is a cost savings to regulated entities. This is because the requirements to meet the eligibility determination process are less than what is required under registration. In the baseline, or no rule scenario, developers must maintain records related to registration; in the rule scenario, developers must similarly maintain records related to the exemption and exemption eligibility determination process—the net effect therefore of this requirement on developers is zero. In both the baseline, or no rule scenario, and in the rule scenario, developers are subject to the adverse effects reporting requirement—the net effect therefore of this requirement on developers is also zero.

The costs of the rule also include differences to societal welfare as a result of the rulemaking, which in this case would be any increased risk to human health or the environment from the change in regulatory oversight from the rule. There are little to no costs such as these anticipated by the rule because the criteria for qualification were chosen to minimize any such risks. EPA has concluded that adverse effects due to aggregate exposure to residues of pesticidal substances from ''PIPs created through genetic engineering from a sexually compatible plant'' through the dietary, non-food oral, dermal and inhalation routes are highly unlikely.

II. Summary of the Proposed Rule

In a proposed rule issued in October 2020 (Ref. 2), EPA proposed to:

1. Exempt ''plant-incorporated protectants based on sexually compatible plants created through biotechnology'' (40 CFR 174.26) from the requirement of a tolerance under FFDCA and from certain registration requirements under FIFRA, except for the following requirements: a proposed requirement of recordkeeping (40 CFR 174.73), a proposed eligibility determination process (40 CFR 174, subpart E), and the existing adverse effects reporting requirement for exempt plant-incorporated protectants (40 CFR 174.71);

2. Clarify the general qualifications for exemption for plant-incorporated protectants at 40 CFR 174.21;

3. Clarify how the proposed exemption relates to the existing exemption for plant-incorporated protectants derived from sexually compatible plants at 40 CFR 174.25; and

4. Allow the existing inert ingredient exemption at 40 CFR 174.705 to include biotechnology.

Unit VI. of the proposed rule explained the proposed exemption for ''PIPs based on sexually compatible plants created through biotechnology,'' detailed the rationale underlying that proposal, and described associated definitions that were proposed for codification or amendment (85 FR 64308) (Ref. 2), and also described the two primary considerations that EPA believed together would constitute the basis for meeting the FIFRA section 25(b)(2) standard for exemption (the pesticidal substance is found in plants that are sexually compatible with the recipient plant; and limitations on the expression profile). Also described were the details of the proposed eligibility determination process, and a proposed recordkeeping requirement for

exempted PIPs listed under 40 CFR 174.21(d).

In addition, EPA proposed edits to 40 CFR 174.21 to clarify the applicability of this framework to other PIP exemptions and EPA proposed to clarify the relationship between the proposal on ''PIPs based on sexually compatible plants created through biotechnology'' and the exemptions currently at 40 CFR 174.25, ''Plant-incorporated protectant from sexually compatible plant,'' and 40 CFR 174.508, ''Pesticidal substance from sexually compatible plant; exemption from the requirement of a tolerance.'' EPA also proposed to allow the existing inert ingredient exemption at 40 CFR 174.705 to include inert ingredients created using biotechnology so long as they still meet the existing criteria.

III. Summary of the Final Rule

In this action, EPA is finalizing the following:

1. An exemption for a category of ''PIPs created through genetic engineering from a sexually compatible plant;''
2. An exemption for a category of ''loss-of-function PIPs;''
3. An exemption eligibility determination process for certain exempted PIPs, including exemption specific information required for submission to support the exemption;
4. Recordkeeping requirements for certain exempted PIPs;
5. Clarifications for the general qualifications for exemption at 40 CFR 174.21;
6. Clarifications on the relationship between the existing exemptions for PIPs from sexually compatible plants and the newly issued exemption for ''PIPs created through genetic engineering from a sexually compatible plant;'' and
7. Allow the existing inert ingredient exemption at 40 CFR 174.705 to include genetic engineering.

A. Exemption for ''PIPs Created Through Genetic Engineering From a Sexually Compatible Plant''

This rule exempts from all FIFRA requirements, except for the adverse effects reporting requirements at 40 CFR 174.71, the recordkeeping requirements at 40 CFR 174.73 (as specified in 40 CFR 174.21(d)), and the eligibility determination process outlined in subpart E, ''PIPs created through genetic engineering from a sexually compatible plant.'' In the proposed rule, PIPs described under 40 CFR 174.26 were termed ''PIPs based on sexually compatible plants created through biotechnology.'' In this final rule, EPA has updated the name of the PIPs described under 40 CFR 174.26 to be ''PIPs created through genetic engineering from a sexually compatible plant'' based on public comment, as discussed in Unit IV.A.3.

1. Associated Definitions

The language describing the exemption appears in 40 CFR 174.26. Pertinent definitions associated with the exemption are found in 40 CFR 174.3 and include:

''*Gene*'' and other grammatical variants such as ''genic,'' means a unit of heritable genetic material that is comprised of the genetic material necessary for the production of a substance.

The definition for ''gene'' was revised from the proposal to remove the word ''functional'' before the phrase ''unit of heritable genetic material that is comprised of the genetic material necessary for the production of a substance.'' EPA made this change because loss-of-function traits are created by targeting a gene underlying an unwanted trait by reducing or removing the gene's function. While the gene may no longer be functional, structurally it is still a gene. Although this is commonly understood in the scientific community, removing the word ''functional'' from the definition may reduce confusion over the relationship between the definition of ''gene'' and ''loss-of-function PIPs.'' Therefore, for the reasons outlined, EPA removed the word ''functional'' from the definition of ''gene.'' As discussed in Unit V.A. of the proposal, the two genic regions relevant to the exemptions under 40 CFR 174.26 are the coding and regulatory regions. These regions are delineated through use of the phrase ''genetic material necessary for the production,'' which as defined under 40 CFR 174.3 means both ''genetic material that encodes a substance or leads to the production of a substance; and regulatory regions. It does not include noncoding nonexpressed nucleotide sequences.'' ''Noncoding, nonexpressed nucleotide sequences'' is also defined under 40 CFR 174.3 and includes examples such as linkers, adapters, homopolymers, and sequences of restriction enzyme recognition sites (further discussed in the context of these exemptions in Unit IV.B.1.).

''*Genetic engineering*'' means the modification of the genome of an organism using recombinant, synthesized, or amplified nucleic acids or other techniques excluded from the definition of conventional breeding. ''Genome'' is a defined term in 40 CFR 174.3 which means ''the sum of the heritable genetic material in the plant, including genetic material in the nucleus and organelles.'' EPA believes the use of the defined word ''genome'' in the ''genetic engineering'' definition would capture genetic engineering edits resulting in modifications to the proteome or transcriptome that are stably heritable.

As discussed in Unit IV.A.2., EPA received a comment suggesting a definition for ''biotechnology.'' However, for consistency across the Coordinated Framework, the Agency chose to instead define ''genetic engineering.'' EPA used the two phrases synonymously in its proposed rule and therefore does not consider the change from ''biotechnology'' to ''genetic engineering'' to be substantive. For additional discussion on maintaining consistency across the Coordinated Framework for exemptions of products derived from genetic engineering, see Unit III.H.: ''Alignment of the proposed rule with USDA's amendment to 7 CFR 340'' of the Response to Comments document in the docket associated with this rulemaking.

''*Native allele*'' means a variant of a native gene that is identified in the genetic diversity of plants sexually compatible with the recipient plant.

''*Native gene*'' means a gene that is identified in the recipient plant or source plants that are sexually compatible with the recipient plant. It does not include genes introduced through genetic engineering from a source organism that is not sexually compatible with the source plant.

The definition for ''native gene'' was revised from the proposal based on public comment (Unit IV.A.1.). In the proposal, rather than specifically excluding genes introduced through recombinant DNA or similar techniques from a non-sexually compatible source organism, EPA used the term ''never derived.'' EPA received comment suggesting that a greater focus on excluding transgenes (*i.e.,* genes introduced from non-sexually compatible organisms) may aid in clarity and in turn reduce uncertainty around genes originating through natural horizontal gene transfer. EPA agreed with the suggestion and revised the definition to state EPA's intent more explicitly as outlined in the proposed rule (*i.e.,* to exclude substances that conventional plant breeders do not have experience with, such as a bacterial endotoxin not historically found in a food plant). Screening practices and analyses performed as part of the standard conventional breeding process serve to eliminate plants that raise safety, quality or performance concerns. By limiting exempt substances to those

in which conventional plant breeders have experience, EPA can have confidence that these conventional plant breeding practices would still be protective for substances of exempt PIPs.

In addition, EPA revised the definition in 40 CFR 174.3 for ''*Sexually compatible.*'' In the proposed definition EPA stated that ''a viable zygote can be formed.'' This phrase was minorly revised to state ''plants must be capable of forming a viable zygote'' for clarity.

2. Exemption Criteria

PIPs that are created through genetic engineering but that could have otherwise been created through conventional breeding are exempt (40 CFR 174.26). The exemption criteria and associated definitions circumscribe PIPs that are created through genetic engineering using knowledge of nucleotide sequences in sexually compatible source plants to re-create a native allele or other functional nucleotide sequence identical to that which is found in a source plant. This would enable the use of genetic engineering of clonally-propogated cultivars of crops such as potato, grape, tree fruits, etc., to recreate pesticidal alleles found in sexually compatible cultivars or crop wild relatives. The exemption specifies criteria regarding the types of modifications that are allowed to be made to ensure that the exempt PIPs are characteristic in identity and in expression profile to those found in conventionally bred plants, and are therefore substances with which conventional plant breeders and conventional plant breeding screening methods have experience.

The scope of ''PIPs created through genetic engineering from a sexually compatible plant'' is delineated in 40 CFR 174.26(a). The regulatory text identifies two overarching categories that specify what will qualify as an exempt PIP pesticidal substance: (1) The insertion of new genetic material and (2) The modification of existing genetic material.

The provision at 40 CFR 174.26(a)(1) allows for insertions of new genetic material into the recipient plant so long as the genetic material is a native gene that is found in the sexually compatible plant population of that plant. This category requires that the entire pesticidal substance (*e.g.,* amino acid sequence for proteinaceous PIPs) that is created from the native gene be identical to that produced in the source plant. 40 CFR 174.26(a)(1) was revised from the proposed text to include a criterion related to inserted regulatory regions. 40 CFR 174.26(a)(1) now requires that any regulatory regions inserted as part of the native gene be identical to the regulatory regions of the native gene identified in the source plant. This change was made in response to comments EPA received stating that the proposed criterion related to expression profile (proposed 40 CFR 174.26(b)) was unclear (Units IV.C.2. and IV.E.4.b.). In response to these comments, EPA instead now provides specific criteria at codified 174.26(a)(1) related to the types of modifications that may impact expression. EPA is aware that intronic regions of genes may exhibit regulatory functions, but EPA does not expect that all introns necessarily need to be inserted as part of a native gene. Therefore, when describing the criterion related to identical sequences in the regulatory regions, EPA used the phrase ''regulatory regions inserted as part of the native gene,'' to specify that the criterion only applies to those regulatory regions that are ultimately inserted as part of the native gene (*i.e.,* it is not required that all regulatory regions be inserted, but those that are inserted must meet the criterion).

The final text in 40 CFR 174.26(a)(1) was revised from what was in the proposed text to remove the clause ''into a non-genic location'' in the phrase ''A native gene is engineered into a non-genic location of the recipient plant genome [. . .].'' In the proposal, EPA stated that this phrase was intended to preclude the insertion of the native gene into an existing gene to prevent the production of a novel substance (*e.g.,* a partial or modified substance) by the existing gene. However, upon further evaluation of this clause, prompted by public comment (Response to Comments document Unit III.A.3.), EPA determined that this restriction is not necessary as any novel substance that would be produced as a result of a fusion with the inserted PIP gene (*i.e.,* through the creation of a novel open reading frame), would not meet the exemption under 40 CFR 174.26.

The provision at 40 CFR 174.26(a)(2) describes permissible modifications to the existing genetic material in the recipient plant. 40 CFR 174.26(a)(2) allows for modifications of the existing native gene to match corresponding polymorphic sequence(s) in a native allele of that gene using a single source plant as a template. Polymorphisms are variants of a gene sequence that are shared between native alleles. These genetic variations may be composed of single nucleotides (*i.e.,* Single nucleotide polymorphisms (SNPs)) or larger DNA segments and they are found at the same locus within the genetic sequence of two or more native alleles. In some cases, enhanced pesticidal properties of a gene product can be attributed to one or more of these genetic variations within a native gene (Refs. 5, 6). The final rule (see 40 CFR 174.26(a)(2)) allows developers to utilize their knowledge of specific polymorphisms in regulatory and coding regions of native alleles to make changes to the native gene in their recipient plant. The phrase ''using a single source plant as a template'' in the provision limits the number of source plants for the polymorphic sequences to one. For example, it is not permissible to modify the polymorphic sequence of a native gene (in the recipient plant) to match a polymorphic sequence found in the native allele of a source plant and also modify a second polymorphic sequence in the native gene to match a sequence found in the native allele of a different source plant. This requirement is because EPA believes that increasing the amount of plants used as source plants for a single PIP may also lead to an increase in the likelihood that the substance is altered to something that plant breeders may not have experience. The second part of the phrase ''as a template'' indicates that the polymorphism that is engineered into the recipient plant must be identical in sequence to that which is found in the native allele of the source plant.

The final rule (see 40 CFR 174.26(a)(2)) differs from what was proposed at 40 CFR 174.26(a)(2)(ii) in that EPA previously proposed to require that modifications resulting in a native allele produce a pesticidal substance identical to that produced in the source plant. The exemption category at 40 CFR 174.26(a)(2) is promulgated in response to comments received indicating that the proposed exemption categories were too narrow in that they do not capture the full extent of genetic variation that can occur in plants (Unit IV.C.1.). While the final text in 40 CFR 174.26(a)(2) does not require the entire substance to be identical to a substance found in the sexually compatible population of the recipient plant, it does require the individual polymorphism(s) to have been identified. By requiring the polymorphic sequences to be identical, this new exemption category allows the Agency to capture more of the possible genetic variation that can occur in plants, while staying within the bounds of what could have been achieved through conventional breeding and what was proposed.

EPA acknowledges that the genetic variation that is observed in plants has the potential to be greater than what is captured at 40 CFR 174.26(a). Therefore, the Agency intends to revisit the

question of capturing a broader range of genetic variation under 40 CFR 174.26 in the future; a new rulemaking process that would be initiated by the Agency if, for example, new scientific information becomes available or if prompted by an interested party through an Agency inquiry, *e.g.,* based on a specific PIP product. Importantly, any new categories of exempt PIPs that would be added to 40 CFR 174.26 through this process in the future: (1) Would be required to fall within the previously defined scope of exempt PIPs, *i.e.,* those that can be created through conventional breeding; (2) Would be subject to recordkeeping requirements and documentation for exemption (Unit III.D.); and (3) Would at least initially be subject to the EPA confirmation process (Unit III.C.3.). By adhering to these requirements, EPA can ensure that any future categories of PIPs created through genetic engineering from sexually compatible plants will remain within the scientific scope that was presented in the proposal, and that underlies the current exemptions at 40 CFR 174.26, and that these categories would remain subject to the procedural guard rails set in place by the eligibility determination process.

The proposed regulatory text included additional categories that are not being finalized under 40 CFR 174.26. To increase clarity, the category encompassing ''loss-of-function PIPs'' that was proposed at 40 CFR 174.26(a)(2)(iv) has been removed and a new, stand alone exemption for ''loss-of-function PIPs'' at 40 CFR 174.27 was created in its place (Unit III.B.). Proposed 40 CFR 174.26(a)(2)(i) allowed for regulatory region modifications so long as the pesticidal substance remained unchanged, but relied on proposed 174.26(b) to specify the bounds of the expression profile. However, EPA received public comment stating that the criterion related to expression profile at proposed 40 CFR 174.26(b) was unclear (Units IV.C.2. and IV.E.4.b.). In response to these comments, 40 CFR 174.26(a)(2) now includes a criterion related to inserted regulatory region modifications (*i.e.,* must match corresponding polymorphic sequences in a native allele), therefore making proposed 40 CFR 174.26(a)(2)(i) redundant. Because proposed 40 CFR 174.26(a)(2)(i) was removed, proposed 40 CFR 174.26(a)(2)(iii) was also removed as it was dependent on proposed 40 CFR 174.26(a)(2)(i). Proposed 40 CFR 174.26(a)(2)(ii) is effectively a subset of what is possible under codified 40 CFR 174.26(a)(2), and is therefore not finalized. Finally, proposed 40 CFR 174.26(b) previously specified expression profile bounds, but due to public comment, EPA now includes specific criteria related to allowable modifications that could impact expression in the subsections of 40 CFR 174.26(a), thereby making proposed 40 CFR 174.26(b) unnecessary.

EPA does not believe that the removal of the proposed categories from the final regulatory text at 40 CFR 174.26 reduces the scope of PIPs exempted through this rulemaking since proposed 40 CFR 174.26(a)(2)(iv) is now being finalized as 40 CFR 174.27, proposed 40 CFR 174.26(a)(2)(ii) represents a subset of what can be accomplished under codified 40 CFR 174.26(a)(2), and since proposed 40 CFR 174.26(a)(2)(i) and proposed 40 CFR 174.26(a)(2)(iii) were deemed redundant.

The final text of 40 CFR 174.26(b) states that the requirements in 40 CFR 174.21(d) (*i.e.,* the recordkeeping requirements and the eligibility determination procedures) must be met in order for the exemption to apply. This is minorly revised from the proposed regulatory text which stated that the ''exemption does not apply until the requirements in subpart E of this part have been met;'' however, the recordkeeping requirements are located in subpart D, and therefore citing to 40 CFR 174.21(d) is a more streamlined citation.

In addition to exempting the active ingredient of PIPs created through genetic engineering from sexually compatible plants from the requirements of FIFRA, EPA is also finalizing the exemption for residues of these substances from the requirement of a tolerance under the FFDCA at 40 CFR 174.541. The exemption criteria are identical to those at 40 CFR 174.26 except that in order to be exempted from the requirements of a tolerance, residues of the pesticidal substance must also not be present at levels that are injurious or deleterious to human health (40 CFR 174.541(b)). The ''injurious or deleterious'' language is included in this rule to align with the same criteria found in 40 CFR 174.508 for residues of PIPs in sexually compatible plants. (*https://www.govinfo.gov/content/pkg/FR-2001-07-19/pdf/01-17983.pdf*). This language was adopted in the 2001 rule in response to comments about the potential for naturally occurring compounds to be present in foods at hazardous levels and to be more consistent with FDA policy and the standard applied to evaluate adulterated food: ''food shall be deemed to be adulterated . . . if it bears or contains any poisonous or deleterious substance which may render it injurious to health. . . .'' 21 U.S.C. 342(a)(1). The purpose of this language was to allow expeditious removal of the offending food from the market if injurious or deleterious levels of a substance were present in food. All of the criteria in 174.541 must be met: the conditions in paragraph (a) limit the identity of the substance, the condition in paragraph (b) set limits on the level of expression in the plant, and the conditions in paragraph (c) ensure the application of the exemption is properly documented. Regarding the condition in paragraph (b), one example of how this might work is if a source plant were to produce a pesticidal substance at levels that are injurious or deleterious to human health, that PIP would not qualify for exemption if the level of expression in the recipient plant matched the injurious or deleterious levels seen in the source plant. It is also important to note that EPA considers multiple native gene insertions of the same gene to be one PIP (further discussed in Unit IV.B.2.), 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. Developers modifying or inserting genes that produce substances with sequence homology to known mammalian toxins, toxicants, or allergens should ensure that the levels of pesticidal substances are within the ranges of levels generally seen in plant varieties currently on the market and known to produce food safe for consumption (*i.e.,* ensure that their levels are not injurious or deleterious to human health). Such substances expressed above these levels would likely trigger additional review during the EPA confirmation and may not fit the exemption criteria.

Additionally, 40 CFR 174.541(c) has been edited to more specifically cite to 40 CFR 174.90, rather than the entire subpart E. This citation is different from that found at 40 CFR 174.26(b) due to a difference in statutes. Specifically, 40 CFR 174.26(b) cites to 40 CFR 174.21(d), which describes the general qualifications for exemption under FIFRA, whereas 40 CFR 174.541 is an exemption from the requirement of a tolerance under FFDCA and therefore would not cite to exemption qualifications under FIFRA. Because the regulatory text at 40 CFR 174.26 for the active ingredient of ''PIPs created through genetic engineering from a sexually compatible plant'' and the corresponding tolerance exemption for residues of these active ingredients at 40 CFR 174.541 are identical (except for

the two clauses discussed in this paragraph) all other changes to the regulatory text that were discussed for 40 CFR 174.26 in this Unit were also applied to 40 CFR 174.541.

B. Exemption of ''Loss-of-Function PIPs''

This rule exempts ''loss-of-function PIPs'' from all FIFRA requirements, except for the adverse effects reporting requirements at 40 CFR 174.71, the recordkeeping requirements at 174.73 (as specified in 40 CFR 174.21(d)), and the eligibility determination process outlined in subpart E. The exempt PIPs represent a subcategory of PIPs described in the proposed rule (Ref. 2). In this final rule, EPA is creating a separate exemption for ''loss-of-function PIPs,'' which allows the Agency to create criteria specific to these types of PIPs and an accompanying definition for increased clarity. EPA made this change in response to comments that indicated the need for greater clarity and the broadening of the exemption text related to ''loss-of-function PIPs'' regarding the identicality of the substance (Unit IV.D.2.). As discussed in Unit IV.D.1., the modified genetic material of a ''loss-of-function PIP'' constitutes both the pesticidal substance and the active ingredient. The language describing the exemption appears in 40 CFR 174.27.

1. Associated Definitions

Because EPA is creating a separate exemption for ''loss-of-function PIPs,'' EPA is also codifying a definition associated with the exemption in 40 CFR 174.3:

''*Loss-of-function plant-incorporated protectant*'' means a plant-incorporated protectant in which the genetic material of a native gene is modified to result in a pesticidal effect through the reduction or elimination of the activity of that gene. For purposes of loss-of-function plant-incorporated protectants, the active ingredient and pesticidal substance are one and the same and are defined as the genetic material that has been modified to create the pesticidal trait (*i.e.,* modification of the sequence of nucleic acids). Loss-of-function plant-incorporated protectants do not include instances where the reduction or elimination of the activity of the modified native gene results in the intentional increase of activity of another pesticidal gene.

The first sentence of this definition specifies that for a PIP to be considered a ''loss-of-function PIP,'' a pesticidal effect must be created through the genetic modification of a native gene, which then leads to the reduction or elimination of the activity of that native gene. The second sentence defines the regulated substance (see Unit IV.D.1. for additional discussion). The third sentence explicitly excludes the scenario in which a modification of a native gene not only leads to the reduction in the expression of that native gene, but additionally leads to an increase of activity of another, ''secondary'' gene, with that ''secondary'' gene then conferring the pesticidal activity (*e.g.,* the altered gene encodes for a repressor whose absence does not itself lead to a pesticidal effect but rather the increased expression of a second gene that encodes a pesticidal substance). This definition is consistent with the description of ''loss-of-function PIPs'' in Unit VII.E. of the proposed rule (Ref. 2).

2. Exemption Criteria

Both the definition at 40 CFR 174.3 and the exemption text at 40 CFR 174.27 focus on the loss-of-function trait that results from the modification (*i.e.,* the reduction or elimination of the activity of the modified gene), and do not include requirements related to source plants or limit the location within the gene to which modifications are allowed to be made (*i.e.,* regulatory region or coding region). Specifically, 40 CFR 174.27 specifies two requirements, the first of which at 40 CFR 174.27(a) is almost identical in language to the loss-of-function definition and specifies that the genetic modification must result in a ''loss-of-function PIP.'' The type of genetic modification to a native gene that results in the loss of activity of that gene is not relevant so long as a ''loss-of-function PIP'' is the result of that modification. As with the exemptions at 40 CFR 174.26, the second requirement at 40 CFR 174.27(b) specifies that the exemption for ''loss-of-function PIPs'' only goes into effect after the requirements for the eligibility determination in 40 CFR 174.21(d) have been met.

In the proposed rule, ''loss-of-function PIPs'' were a subcategory under 40 CFR 174.26 (specifically proposed 40 CFR 174.26(a)(2)(iv)), and they were held to the same ''identical substance'' criterion as other PIPs described in proposed 40 CFR 174.26. While the EPA does not find that it can make an *a priori* safety determination under FIFRA and FFDCA for non-identical pesticidal substances now exempted under 40 CFR 174.26 (Unit IV.C.1.), it finds that no such restriction is warranted for ''loss-of-function PIPs'' under 40 CFR 174.27 (Unit IV.D.2.). This conclusion is based on characteristics of ''loss-of-function PIPs,'' the common occurrence of pesticidal traits resulting from the loss-of-function of endogenous genes in conventional breeding, and the biological processes that all proteins undergo within plants (Unit IV.D.2.).

The absence of function is a hallmark of ''loss-of-function PIPs,'' *e.g.,* loss of the activity of a native gene that would otherwise facilitate the susceptibility of that plant to a pathogen. Importantly, the criteria and definition state that for a ''loss-of-function PIP,'' the native gene modification results in a pesticidal effect from the reduction or elimination of the activity of *that* gene. This indicates a direct cause-and-effect relationship between the reduction in the expression of a specific native gene and a pesticidal effect. This direct cause-and-effect relationship also means that not all modifications that lead to a loss-of-function of a gene and that result in a pesticidal effect are considered ''loss-of-function PIPs.'' For example, this scenario may occur if a modification of a native gene not only leads to the reduction in the expression of that native gene, but also to an increase of the activity of *another,* ''secondary'' gene, with that ''secondary'' gene then conferring the pesticidal activity (*e.g.,* the altered gene encodes for a repressor protein whose absence does not itself lead to a pesticidal trait but rather the increased expression of a second gene that encodes a pesticidal substance). Because in this instance there is no direct cause-and-effect relationship between the reduction of the expression of the modified native gene and the pesticidal effect, that gene modification and resulting ''secondary'' activity would not be considered a ''loss-of-function PIP'' under 40 CFR 174.27. Further, in the scenario described, that gene modification and resulting ''secondary'' activity would only be exempt under the new regulations if it meets the criteria outlined in 40 CFR 174.26 and from FFDCA if the residues meet the requirements under 40 CFR 174.541. For ''loss-of-function PIPs,'' EPA clearly indicates the requirement for this direct cause-and-effect relationship of native gene modification and the pesticidal effect in the second sentence of the ''loss-of-function PIP'' definition.

C. Eligibility Determination Process

The Agency is finalizing subpart E, which includes provisions describing the eligibility determination process and documentation required for an exemption of certain PIPs. Specifically, in order for a PIP listed under 40 CFR 174.21(d) to be eligible for exemption, an exemption eligibility determination must be completed prior to engaging in

FIFRA-regulated activities. EPA agrees with commenters arguing that requiring an eligibility determination will provide additional clarity to developers of PIP products under certain circumstances and increase transparency and public trust in products containing these PIPs (Unit IV.E.1.). The primary difference between the proposal and the final rule is the restriction of the self-determination option to only certain PIPs exempted by this rulemaking. In the proposal, all exempted PIPs had the option of self-determination. However, in the final rule, only developers of ''loss-of-function PIPs'' (40 CFR 174.27) currently have the option to self-determine whether the exemption criteria are met. To that end, modifications were made to proposed 40 CFR 174.90, 40 CFR 174.91, and 40 CFR 174.93 (Units III.C.1., C.2., and C.3.). In addition, the titles of these three subsections were minorly revised from the proposal for clarity.

Given the straightforward criteria describing ''loss-of-function PIPs'' (*i.e.,* a focus on function rather than source plant or underlying sequence), EPA believes it is appropriate for ''loss-of-function PIPs'' to be eligible for the self-determination option as it is unlikely for a developer to accidentally misdetermine exemption eligibility of these PIPs. Additionally, the mode of action of ''loss-of-function PIPs'' (*i.e.,* reduction or elimination of an endogenous gene) is fundamentally different from ''PIPs created through genetic engineering from a sexually compatible plant'' (*e.g.,* intentional production of a pesticidal protein), and as such, further lends itself to the availability of a self-determination option. 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.

A separate determination of eligibility of exemption for purposes of the FFDCA exemption for a PIP proposed for use in food or feed is required only if that determination has not already been submitted under FIFRA. This is because the exemption eligibility determination process described in 40 CFR 174.21 already requires the applicant to certify that the PIP meets the general qualifications for exemption, which includes exemption under the FFDCA for PIPs used in food or feed. A scenario in which a developer will need an exemption eligibility determination specifically for the purposes of FFDCA, but not FIFRA, would be when residues of a PIP are in or on food imported into the United States, but the PIP is not intended to be sold or distributed for pesticidal use (*e.g.,* PIP-containing seed or plant sold for planting) in the United States (and thus is not subject to FIFRA regulation). Additional discussion on the types of activities that warrant an eligibility determination can be found in Unit IV.E.5.

1. Determining Eligibility

Regarding the process of an exemption eligibility determination under 40 CFR 174.90, this provision states at 40 CFR 174.90(a) that, depending on the applicable exemption, developers have two, non-mutually exclusive options to notify EPA that their PIP meets the exemption criteria: (1) Seek EPA confirmation that a PIP meets the exemption criteria, and (2) Submit a self-determination letter that a PIP meets the exemption criteria. For PIPs subject to the eligibility determination process, an EPA confirmation is mandatory unless the PIP is listed at 40 CFR 174.90(a)(2) as eligible for the self-determination option. For PIPs eligible for the self-determination option, an EPA confirmation can be sought instead of, in conjunction with, or subsequent to the submission of the self-determination letter.

As stated in Unit III.C., only ''loss-of-function PIPs'' under 40 CFR 174.27 are currently eligible for the self-determination option and no ''PIPs created through genetic engineering from a sexually compatible plant'' under 40 CFR 174.26 are currently listed under 40 CFR 174.90(a)(2). Therefore all ''PIPs created through genetic engineering from a sexually compatible plant'' are required to undergo an EPA confirmation process. However, EPA intends to reconsider this in future rulemakings, and as such, EPA has codified text at 40 CFR 174.90(a)(2)(ii) to accommodate this possibility.

The provision explains at 40 CFR 174.90(b) that submissions for a request for EPA confirmation or a letter of self-determination must be made electronically, which means that they may not be made by mailing the information in physical form to the Agency (*e.g.,* sending hard copies or data storage devices such as DVD). Specifically, electronic submissions are required to be made through EPA's electronic submission portal which receives legally acceptable data in a secure manner (see Unit IV.E.6. for additional discussion). That system is used, amongst other things, for submission of pesticide registration applications, and will now additionally accommodate the eligibility determination processes associated with the PIPs identified in this rule. The electronic submission process will accommodate submissions when the final rule is effective, specifically, 60 days after the date of publication in the **Federal Register**. This electronic submission process differs from the proposal, which included instructions on how to submit a self-determination or confirmation request via physical mail. Guidance for electronic submission can be found in Pesticide Registration Notice 2011–3 (Ref. 7) or any subsequent revision or replacement. The provision at 40 CFR 174.90(c) also explains the procedures that must be followed to claim information submitted as confidential.

For PIPs that are eligible for both the self-determination and EPA confirmation options, the provision at 40 CFR 174.90(d) further explains the relationship between the EPA confirmation processes and a letter of self-determination. Specifically, if a developer chooses to request EPA confirmation in accordance with 40 CFR 174.93 in conjunction with or subsequent to submitting a self-determination letter in accordance with 40 CFR 174.91, the exemption is effective from the time the company receives confirmation of submission of the self-determination letter. The exemption remains effective if EPA affirms the developer's determination that the PIP meets the exemption criteria and the self-determination is superseded by EPA's written confirmation in response to the confirmation request. Alternatively, in instances in which no prior self-determination has been provided to the Agency in accordance with 40 CFR 174.91, and the developer submits a request for confirmation to the Agency, the exemption applies only once EPA provides written notice to the developer confirming that the PIP meets the criteria for exemption.

The provision also includes text at 40 CFR 174.90(e) stating that EPA reserves the right to assess or revisit at any time after EPA issues a confirmation of eligibility or the letter of self-determination is submitted, whether a PIP meets, or has met, the criteria for exemption. If EPA finds or has reason to believe that, at any time before or during this review of eligibility for exemption, the product is non-compliant with FIFRA or presents an adverse risk to human health, the environment, or program integrity, the Agency can take immediate steps—including enforcement—to address that non-compliance or to protect against those adverse risks. This is revised from the proposed text to make explicitly clear

that although EPA will generally notify the submitter in writing of EPA's intention to initiate a review of eligibility for exemption, EPA may take such action without first informing the submitter of an eligibility review if the situation warrants.

As exempt PIPs are still subject to 40 CFR 174.71, upon learning of any adverse effects (*i.e.,* that a person or nontarget organism allegedly suffered an adverse effect due to exposure to a PIP), EPA has the authority to evaluate whether the PIP still meets the criteria for exemption. As described in the preamble of the July 19, 2001, **Federal Register** notice implementing 40 CFR 174.71 (66 FR 37772; July 19, 2001; FRL–6057–7) (Ref. 8), reports involving food or feed (*i.e.,* those subject to enforcement under FFDCA) would be made to EPA, but EPA will share such reports with FDA. EPA and FDA will individually determine whether any action, including the possibility of enforcement, is necessary to protect the public health or the environment, and if so, what constitutes appropriate action based on their respective statutes (EPA–FIFRA; FDA–FFDCA). Additional discussion regarding EPA enforcement can be found in Unit III.D.7. of the Response to Comments document found in the docket associated with this rulemaking.

The provision outlines instances at 40 CFR 174.90(f) in which an exemption determination for a PIP can be extended to other PIPs. A determination that a PIP meets the exemption criteria would be required for each modified gene and plant species combination (*e.g.,* PIP ''A'' in corn and PIP ''A'' in tomato would each require their own determination). However, EPA is aware that a plant species can comprise multiple varieties and does not intend for the PIP in each variety to require its own submission. In order to extend the exemption for a PIP, the developer would need to comply with the provisions outlined in 40 CFR 174.21(d) for the first modification in that plant species and that exemption can then be extended in one of two ways. If the exempted PIP is moved through conventional breeding, the exemption is extended to the subsequent PIP. To extend the exemption of the PIP to subsequent genetic engineering events, the PIP must meet exemption-specific criteria outlined by EPA. The paragraph in this text was edited from the proposed rule to explicitly state that movement of exempt PIPs through conventional breeding also results in the extension of exemption status of that PIP and to clarify that the subparagraphs 40 CFR 174.90(f)(1) and 40 CFR 174.90(f)(2) are specific to genetic engineering.

For a ''PIP created through genetic engineering from a sexually compatible plant,'' the exemption extends to subsequent engineering of that PIP by the submitter into other varieties of that same plant species as long as the subsequent PIP produces the identical substance as in the exempt PIP and no new modifications were made to the regulatory regions. For example, if a developer first modifies an existing gene in a tomato variety to create a native allele, this would require a determination; however, if the developer subsequently creates the same native allele in another tomato variety, the developer would not be required to submit a second determination request for the additional variety. For a ''loss-of-function PIP,'' an exemption extends to subsequent engineering of that PIP by the submitter into other varieties of that same plant species as long as the submitter is targeting the same native gene to create the ''loss-of-function PIP.'' This text is modified from the proposal based on a comment arguing that the criteria should focus on the trait phenotype and function (Unit IV.E.2.). As described in Unit IV.D.2., ''loss-of-function PIPs'' now have their own exemption category with a focus on function rather than substance identity, and as such, the extension of the exemption for ''loss-of-function PIPs'' is now described in 40 CFR 174.90(f)(2) with a similar focus.

Finally, EPA has added a new paragraph (g) to 40 CFR 174.90, which explains that a duplicative eligibility submission is not required for purposes of 40 CFR 174.541(c), if it is already being submitted for purposes of 40 CFR 174.21(d). This provision was not in the proposal, but was added for clarification based on public comment (Unit IV.E.5.). Related to these comments, EPA is confirming that the Agency is requiring a separate eligibility determination to be made through EPA's electronic submission portal for residues of those PIPs under 40 CFR 174.541 that are imported into the United States and that are used for food or feed if the developer has not already obtained an exemption under 40 CFR 174.541. This submission includes an acknowledgement that the developer is only submitting an exemption eligibility determination for the purposes of FFDCA but not FIFRA, and therefore it is not permissible for the PIP to be sold or distributed for pesticidal use (*e.g.,* PIP-containing seed or plant sold for planting) in the United States. As discussed in the preamble of the proposed rule, a separate submission of the eligibility determination of the FFDCA exemption for a PIP proposed for use in food or feed is required only if it has not already been submitted under FIFRA.

2. Process for a ''Letter of Self-Determination'' for a PIP To Qualify for an Exemption

This rule finalizes a new provision in subpart E, 40 CFR 174.91, entitled ''Submitting a letter of self-determination'' The provision describes the requirements and process of notifying EPA that the developer has determined (or ''self-determined'') that a PIP qualifies for exemption.

The provision at 40 CFR 174.91 explains that a developer must submit the letter of self-determination prior to engaging in activities that would be subject to FIFRA for the proposed PIP (*e.g.,* distribution and sale of the PIP at issue). As specified in 40 CFR 174.90(b), self-determination letters must be submitted electronically. If a developer does not have an EPA company number, they will be required to obtain one in order to be able to submit a self-determination letter. Self-determination letters will not be submitted under FIFRA section 33 and will not be subject to application fees under the Pesticide Registration Improvement Extension Act of 2022 (PRIA 5). The exemption does not apply until EPA confirms receipt of the self-determination, but since the submission of the self-determination letter will be made electronically, the receipt confirmation by the Agency occurs automatically upon submission and is considered equivalent to written confirmation of receipt.

The provision at 40 CFR 174.91(b) includes information on the required contents of the self-determination letter. This includes a statement certifying the developer's determination of exemption eligibility, the identity of the recipient plant, a unique gene identifier for the native gene, the trait type (*e.g.,* insect resistance), and information on the applicable exemption. The gene identifier is for the native gene (not necessarily the exact sequence of the PIP) and must be from databases curated by the National Center for Biotechnology Information (NCBI), which is part of the National Library of Medicine of the National Institutes of Health (NLM) at the National Institutes of Health (NIH). These databases are available free of charge to scientists globally and will ensure availability of the gene information to EPA and a means to standardize that information. Based on public comment (Unit IV.E.3.), this provision was clarified to explicitly request the identity of the recipient plant, an identifier for the native gene,

and the trait type, rather than the name of the PIP, which may or may not have included such information. Additionally, rather than listing PIP categories eligible for self-determination under 40 CFR 174.91(b)(2) as had been proposed, the provision now cites to the list under 40 CFR 174.90(a)(2). Lastly, EPA streamlined the regulatory text by merging 40 CFR 174.91(b)(4) with 40 CFR 174.91(b)(3) and removing the text of the certification statement from the provisions. The statement is captured in the electronic submission portal and thus listing it in the regulatory text was deemed redundant.

EPA notes that the developer is responsible at all times for ensuring the self-determination is accurate and if at any time EPA determines that a self-determination was fraudulently or incorrectly made, or is no longer accurate due to the availability of new information that was not available at the time the self-determination was made, EPA will notify FDA of this new information, and the Agencies can take action to protect the environment and public health, respectively. This includes the possibility of enforcement under FIFRA or FFDCA.

3. Process To Obtain an EPA Confirmation That a PIP Qualifies for Exemption

This rule establishes a new provision in subpart E entitled ''Requesting EPA confirmation'' (40 CFR 174.93), which describes the process through which a developer may seek confirmation from EPA as to whether a PIP meets the criteria for exemption codified in 40 CFR 174.21. A developer must submit information as outlined in 40 CFR 174.91 along with specific supporting documentation. For example, the information required to support the request for a ''PIP created through genetic engineering from a sexually compatible plant'' is described in 40 CFR 174.95 and discussed in Unit III.C.4.a.

In addition, the provision at 40 CFR 174.93 explains that upon receipt of the request, EPA will review the submission and determine whether the PIP meets all necessary criteria to be exempt under 40 CFR 174.21. The Agency will notify the submitter in writing of its determination. The exemption goes into effect only once the developer receives EPA's confirmation in writing, unless a self-determination letter was previously submitted. As discussed in Unit III.C.1., EPA reserves the right to reassess whether a PIP meets the criteria for exemption should the Agency learn of relevant information subsequent to confirming its eligibility to be exempt under 40 CFR 174.21.

Requests for EPA confirmation are to be submitted using the submission category (M009) and associated fee structure for a Non-FIFRA Regulated Determination under FIFRA section 33 (PRIA). The logistics of the submission for a request and EPA review times may change in the future if PRIA changes or a different structure for submissions is adopted.

4. Documentation for an Exemption

a. PIPs Created Through Genetic Engineering From Sexually Compatible Plants

The rule finalizes the documentation needed for an exemption for ''PIPs created through genetic engineering from a sexually compatible plant.'' There are four main information elements associated with the required documentation, which capture the: (1) Biology of the plant; (2) Description of how the trait was engineered into the plant; (3) Molecular characterization of the PIP; and (4) Information on the history of safe use for those PIPs that are either known mammalian toxins or toxicants or that are from a source plant that is a wild relative of the recipient plant. Collectively, this information allows EPA to ensure that a PIP meets the exemption criteria at 40 CFR 174.26 and 40 CFR 174.541.

The first element (40 CFR 174.95(a)) requires information on the biology of the plant and has two components: (1) The identity of the recipient plant, including genus and species; and, if the PIP was derived from another plant species, the identity of the source plant, including genus and species; and (2) Information to support that the recipient plant and the source plant are sexually compatible. The regulatory text regarding sexual compatibility was minorly revised from proposed ''if the plant-incorporated protectant was derived from another plant species'' to ''if the plant-incorporated protectant was derived from a plant species other than the recipient plant species'' to more directly articulate that this information is only needed if the source and recipient plant are taxonomically classified as belonging to different plant species. As stated in the preamble of the proposed rule (Unit VI.C.4.), to meet this requirement a developer may provide a peer-reviewed literature rationale (*e.g.,* breeding guides, journal articles) instead of generating empirical data to demonstrate that the two plant species are sexually compatible. Therefore, for clarity based on public comment (Unit IV.E.4.a.), the regulatory text regarding sexual compatibility was further modified to replace ''demonstrate'' with ''information to support.''

The second element (40 CFR 174.95(b)) captures information on the pesticidal trait and how it was engineered into the plant. EPA anticipates that this element can be addressed through a narrative description of the intended pesticidal function of the PIP and information on the techniques used to make the genetic modification in the recipient plant (*e.g.,* the molecular tools used, transformation method). The text was revised from the proposal to also require information on the steps that were taken to ensure that no engineering components (*i.e.,* PIP inert ingredients) are expected to remain in the final plant product. Engineering components include, but are not limited to, those associated with the genetic engineering of the plant itself (*e.g.,* Cas protein) and selectable markers that, in the early steps of PIP development, aid in the selection of plant transformants that contain the desired traits (*e.g.,* herbicide resistant markers). Unless the engineering components themselves meet the requirements at 40 CFR 174.705, they would not be exempt inert ingredients. Thus, by requiring this information, EPA will be able to ensure that no unapproved inert ingredients are expected to remain in the final plant product. Similarly, based on public comment (Unit IV.A.2.), EPA has also included a requirement that the developer describe the measures taken to maximize the likelihood that the modification to the recipient plant is limited to the intended modification, including ensuring off-target mutations were minimized (*e.g.,* through the use of *in silico* techniques in guide RNA development). This could be information on the specificity of the endonuclease in the recipient plant species and the use of predictive *in silico* tools that can identify other potential target sites. As discussed in the preamble of the proposed rule (Unit V.A.), by using the definition of a ''gene'' the Agency restricts any genetic modifications made through biotechnology that would fall under the exemption to modifications to the gene itself. Thus, by requiring this information, EPA can determine that this is true.

The third element (40 CFR 174.95(c)) requires information on the molecular identity of the PIP. Specifically, EPA is requiring the sequence of the PIP in the recipient plant and its comparator. This was revised per public comment to clarify the required sequence information, which is based on the

relevant comparator and the type of pesticidal substance (Unit IV.E.4.a.). For example, for native gene insertions the comparator is the sequence of the PIP in the source plant, whereas for native genes that are modified to match corresponding polymorphic site(s), the relevant comparators are the sequence of the PIP in the source plant, the modified recipient plant, and the original native gene in the unmodified recipient plant. What determines the type of sequence information that must be provided is the molecular composition of the pesticidal substance. Nucleic acid sequences must be provided for both native gene insertions and for genes modified to match a corresponding polymorphic site. In addition, if the pesticidal substance is proteinaceous, an amino acid sequence must also be provided. In addition to basic sequence information, if a native allele has been modified according to 40 CFR 174.26(a)(2), then documentation is also required that identifies the modified polymorphic sites within the relevant sequences.

To provide more clarity in response to several comments that were received on the proposal (Unit IV.E.4.b.), EPA has removed the requirement to provide information on the expression profile for those PIPs where the regulatory region has been modified. In the final rule, EPA was able to remove the requirement to provide information on the expression profile because the Agency now includes at 40 CFR 174.26(a) specific criteria related to allowable modifications that could impact expression, thereby restricting expression to what is found in the sexually compatible plant population.

The fourth element (40 CFR 174.95(d)) captures the requirement from proposed 40 CFR 174.95(b) for pesticidal substances that are known allergens or mammalian toxins/toxicants. For these substances, a description of how conventional breeding practices are being used to ensure they do not exceed human dietary safety levels in the recipient food plant must be provided. EPA revised this from the proposed text to specify ''human dietary safety levels'' rather than ''safe levels'' for clarity. EPA also added a clarifying parenthetical, ''ensure residues of pesticidal substance are not present in food at levels that are injurious or deleterious and are within the ranges of levels generally seen in plant varieties currently on the market and/or known to produce food safe for consumption,'' to further define what is meant by ''human dietary safety levels.'' EPA is aware that the conventional breeding process is generally comprised of three stages: trait mapping, trait introgression, and field testing (Ref. 9). Through genetic engineering, the second stage, trait introgression, can occur more quickly and more precisely (*i.e.,* insert only the trait of interest without linkage drag of undesirable traits). However, trait mapping (requires knowledge of plant genetics and biology, likely includes an understanding of any naturally occuring plant toxins) and field testing (evaluates traits related to agronomic parameters, consumer preferences, allergens/toxins/nutrition) are expected to still occur under their normal timeframes. The second component of this section is specific to those PIPs that are from a source plant that is a wild relative, *i.e.,* a non-domesticated relative. 40 CFR 174.95(d)(2) is new and was added as a result of comments that the Agency received on the proposed rule (Unit IV.E.4.a.). For PIPs from wild relatives, a rationale as to why they do not pose a hazard to humans or the environment must be submitted. Several examples of the type of information that can be used to address this requirement are provided in the regulatory text itself.

Information described under elements one through four will inform whether the PIP meets criteria (a) and (b) of the FIFRA exemption and criteria (a) and (b) of the FFDCA exemption for the requirement of a tolerance for residues of PIPs.

b. Loss-of-Function PIPs

This rule also finalizes the documentation needed for an exemption for ''loss-of-function PIPs.'' As discussed in Unit III.B., ''loss-of-function PIPs'' have now been removed as a subcategory from 40 CFR 174.26 and an exemption specific to ''loss-of-function PIPs'' has been created at 40 CFR 174.27. Consequently, establishment of documentation requirements for this PIP category were necessary (40 CFR 174.96). As the ''loss-of-function PIPs'' exemption is focused on phenotype rather than specific underlying nucleic acid sequences, the documentation associated with the exemption is similarly focused on the trait. To this end, the identity of the modified plant (*i.e.,* genus and species) and a description of the pesticidal trait is required (40 CFR 174.96(a)). Along with the description of the pesticidal trait, a description of how the trait was engineered is also required (40 CFR 174.96(b)). This includes a description of the steps that were taken to ensure that no engineering components (*e.g.,* Cas proteins) are expected to remain in the plant and measures taken to maximize the likelihood that the modification to the recipient plant is limited to the intended modification, including ensuring off-target mutations were minimized (*e.g.,* through the use of *in silico* techniques in guide RNA development). This information allows the EPA to ensure the criteria for exemption are met (*e.g.,* no non-exempt inert ingredients remain in the final plant).

D. Recordkeeping Requirements for PIPs Exempt by This Rulemaking

At 40 CFR 174.73, subpart D, EPA is codifying a requirement under FIFRA section 3(a) that any person who is required to submit documentation for the eligibility determination of a PIP under 40 CFR 174.21(d), must maintain documentation of either the request for EPA confirmation or the letter of self-determination (or both, if applicable) along with all supporting documentation for the specific exemption as specified in subpart E. These documents must be maintained for five years starting with the effective date of the exemption. This text is minorly revised from the proposed text for clarity.

E. Clarification of General Qualifications for Exemption

This rule finalizes edits to the ''General Qualifications for Exemptions'' provisions at 40 CFR 174.21 to clarify the applicability of this framework to other PIP exemptions. For paragraph (a), this revision simply clarifies that this paragraph is specific to the active ingredient of the PIP, rather than the PIP as a whole. This is because the definition of a PIP under 40 CFR 174.3 also includes ''any inert ingredient,'' and inert ingredients are not exempt under subpart B but rather subpart X. In the proposed rule, EPA used the phrase ''pesticidal substance'' in its proposed revisions to 40 CFR 174.21(a), while in the final rule, the Agency uses the phrase ''active ingredient.'' The active ingredient definition at 40 CFR 174.3 includes both the genetic material and any pesticidal substance produced (*e.g.,* a protein). Exemption criteria related to both the genetic material and the pesticidal substance are specified in exemptions under subpart B. As such, the titles for the exemptions in subpart B are similarly codified to specify ''active ingredient.''

Paragraph (b) is revised to refer to subpart W, rather than the specific sections and is also revised to specify that the tolerance exemptions apply to the residues of the active ingredient, rather than the PIP as a whole for the same rationale as outlined for the edit

to 40 CFR 174.21(a). It should be noted that although paragraph (b) specifies active ingredient, there are separate tolerance exemptions specific to both the residues of the pesticidal substance (*e.g.,* 40 CFR 174.541) and the genetic material (*i.e.,* 40 CFR 174.507) under subpart W.

Paragraph (c) is revised to refer to subpart X, rather than the specific section of 40 CFR 174.705.

EPA is also finalizing a new paragraph (d) in section 40 CFR 174.21 to accommodate the exemption eligibility determination process (Unit III.C.) and the recordkeeping requirements (Unit III.D.). This paragraph specifies that for PIPs listed in the subsequent subparagraphs, the exemption is contingent upon compliance with recordkeeping requirements and the eligibility determination process. The addition of paragraph (d) does not impact the exemption under section 40 CFR 174.25 for PIPs from sexually compatible plants through conventional breeding as this exemption is not identified in paragraph (d). EPA made two revisions to 40 CFR 174.21(d) since proposal of the rule. First, the Agency added a clarification that 40 CFR 174.73 is implemented ''per sections 8 and 9 of FIFRA (U.S.C. 136f and 136g).'' Those sections of FIFRA specify EPA's inspection authority and impose recordkeeping requirements and they still apply to the PIPs exempted under this rule. Secondly, ''[Reserved]'' was moved to 40 CFR 174.21(d)(3) and replaced in its proposed position at 40 CFR 174.21(d)(2) with ''Loss-of-function plant-incorporated protectants,'' to accommodate the newly created exemption for these types of PIPs at 40 CFR 174.27.

F. Clarification of the Exemption for Sexually Compatible PIPs

The rule finalizes clarifications of the relationship between the newly exempted ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs'' with the previous FIFRA and FFDCA exemptions related to conventionally bred plants (*i.e.,* 40 CFR 174.25 and 40 CFR 174.508). EPA inserted ''created through conventional breeding'' at the end of each section title, and inserted an additional criterion into 40 CFR 174.25 and 40 CFR 174.508, stating that the genetic material is transferred only through conventional breeding. The exemptions at 40 CFR 174.25 and 40 CFR 174.508 have always meant ''only through conventional breeding,'' but this clarification is necessary given the amended definition for ''sexually compatible.''

G. Inert Ingredient Exemption Includes Genetic Engineering

While EPA revised 40 CFR 174.25 and 40 CFR 174.508 to include a criterion specifying that the genetic material is transferred from the source plant to the recipient plant only through conventional breeding, a parallel revision was not proposed or finalized at 40 CFR 174.705.

The amended definition for ''sexually compatible'' states that ''plants must be *capable of forming* a viable zygote through the union of two gametes through conventional breeding'' (emphasis added), which differs from the definition promulgated in 2001 that specified that ''a viable zygote *is formed only* through the union of two gametes through conventional breeding'' (emphasis added). The amendment of the ''sexually compatible'' definition therefore removes the criterion that the gamete formation may only occur through conventional breeding, which would otherwise preclude the use of genetic engineering to create PIPs that are exempt even if those PIPs are moved between sexually compatible plants. Because EPA is not adding an additional conventional breeding criterion to 40 CFR 174.705, like it is for 40 CFR 174.25 and 40 CFR 174.508, the inert ingredient exemption at 40 CFR 174.705 is no longer bound by conventional breeding and therefore allows for the exemption of inert ingredients that are initiated through biotechnology, so long as they still meet the existing criteria of that section.

IV. Discussion of Public Comments and the Agency's Responses

EPA received a total of 8,120 comments on the proposed rule. Of those, 28 were unique and one of those unique comments was supported by 8,093 co-signers. Comments were received from private citizens, industry, academia, professional and trade associations, State regulatory associations, and public interest groups. Of the 28 unique comments, twenty-three were generally supportive of an exemption for PIPs created through biotechnology, while three comments, one of which included the mass mailer, were opposed. An additional two respondents commented on specific aspects of the rule while remaining silent as to their overall position on its promulgation.

In this unit, EPA provides a summary of the major issues raised by commenters and EPA's responses, as well as summaries of public comments that prompted changes to the proposed requirements for the final rule. All public comments and EPA's responses, including those that do not raise significant issues or substantially change the proposed requirements, are included in Response to Comments document (Ref. 1).

A. Definitions and Titles

1. Relationship Between ''Conventional Breeding'' and the Terms ''Native'' and ''Never Derived''

In the proposed rule, EPA sought comment on whether the intent behind the use of the terms ''native'' and ''never derived'' is clear or whether alternative phrasing should be used instead. Most of the commenters that responded to this request stated that EPA's intent was clear but had suggestions on edits to the definitions of ''native gene'' and ''native allele.'' A concern raised by several of the commenters was that alleles that emerged from the use of common conventional breeding techniques, such as induced mutagenesis, may be unintentionally excluded from the definition of ''native allele.'' Thus, some commenters suggested explicitly including the use of induced mutagenesis, embryo rescue, and other conventional breeding techniques in the 40 CFR 174.3 definitions for ''native allele,'' ''native gene,'' ''sexually compatible,'' or ''conventional breeding.'' Another commenter provided an alternative and suggested to focus on the exclusion of transgenes from the native gene definition more explicitly. EPA agreed with the suggestion to focus on the exclusion of transgenes and revised the definition accordingly (Unit III.A.1.). As stated in the proposal, the Agency does not mean to imply that using the term ''native'' would exclude genes originated through conventional breeding techniques like mutagenesis. Native genes comprising the gene pool of sexually compatible plant populations have been developed through the processes of mutation, selection, and genetic exchange. Mutations in any part of a gene can occur naturally or may be induced including through chemical mutagenesis used by plant breeders to create new varieties. Alleles found in sexually compatible plants that may have been created through conventional breeding would be included in the definition of ''native allele'' and ''native gene.'' Additionally, as the requirement does not specify an allele frequency that must be met to qualify as a native allele, identifying one individual with a particular allele is sufficient to claim an allele as a ''native allele.'' EPA also notes that there is no time component of the requirement, and so use of a

native allele identified in a plant from the 1950s, for example, is permissible so long as that plant species is a species known to be sexually compatible with the recipient plant.

Regarding requests to explicitly list conventional breeding techniques like mutagenesis in one of the definitions, EPA does not find this to be necessary, and listing specific conventional breeding techniques may only serve to further cause confusion. EPA finds that the techniques listed in the conventional breeding definition (*e.g.,* bridging crosses and wide crosses) focus on the merging of genetic material from different organisms. Therefore, specific conventional breeding techniques, such as induced mutagenesis, are not explicitly included in the ''conventional breeding'' definition because they are not relevant techniques to the merging of genetic material between organisms.

2. Definition of ''Genetic Engineering''

Two commenters requested that the term ''biotechnology'' be defined. As the regulations have a definition for ''conventional breeding'' under 40 CFR 174.3, which forms the basis for the exemption under 40 CFR 174.25, EPA agrees that it would be prudent to similarly provide a definition to inform the exemption under 40 CFR 174.26. Given that USDA's recent revisions to 7 CFR 340 use the phrase ''genetic engineering,'' EPA chose to define ''genetic engineering'' rather than ''biotechnology,'' to provide consistency across the Coordinated Framework (Ref. 3). EPA thusly updated the term used in the exemption title to be ''genetic engineering.'' EPA used ''genetic engineering'' and ''biotechnology'' synonymously in its proposed rule as evidenced by Unit VI.A.3.g. titled ''Are there any considerations associated with newer biotechnology techniques?,'' where EPA discussed genetic engineering techniques like clustered regularly interspaced short palindromic repeats (CRISPR), zinc-finger nucleases, transcription activator-like effector nucleases, and oligonucleotide-directed mutagenesis.

EPA also received comments requesting the Agency limit the definition of ''genetic engineering'' and therefore the exemptions at 40 CFR 174.26 and 40 CFR 174.27 to high precision techniques such as CRISPR. The Agency has chosen to adopt a broader definition of ''genetic engineering,'' which is more consistent with the dictionary definition of the term. Although the exemptions at 40 CFR 174.26 and 40 CFR 174.27 are not restricted to specific genetic engineering techniques, the exemption criteria in the provisions themselves inherently limit the types of techniques which are likely to be used. For example, it is unlikely for a developer to be able to make the modifications described in 40 CFR 174.26(a)(2)(i) or 40 CFR 174.26(a)(2)(ii) using techniques other than high precision technologies.

Commenters also pointed out that such high precision techniques can be used to limit potential off-target effects from genetic engineering. EPA agrees with the commenters that existing gene editing technologies can be used in a manner to limit off-target effects (*e.g.,* through the use of *in silico* analyses in guide RNA development), and EPA notes that it is expected that the majority of developers already use these types of techniques (Ref. 10). Rather than explicitly limiting the exemption to specific gene modifying techniques, such as CRISPR, the Agency has added an item in the documentation required for developers in 40 CFR 174.95 to describe the measures taken to maximize the likelihood that the modification to the recipient plant is limited to the intended modification (Unit III.C.4.a.). As noted, it is anticipated that developers are already utilizing basic measures to reduce off-target effects, and as such, EPA does not anticipate that this requirement for a description would be unduly burdensome.

3. Title of the Exemption, Name of Exempted PIPs

EPA received comments related to various aspects of the name EPA chose for PIPs proposed for exemption under 40 CFR 174.26. One commenter requested that EPA move the clause ''created through biotechnology'' to directly follow ''PIP.'' The concern was that the original phrasing of ''PIPs based on sexually compatible plants created through biotechnology'' may suggest that the plant has been modified to be sexually compatible, rather than the intended requirement that the resulting PIP be based on a PIP from a sexually compatible plant. EPA agreed with this comment and reordered the clauses as suggested for clarity.

B. Clarification on Allowable Modifications

1. Noncoding, Nonexpressed

EPA received several comments requesting clarification as to whether the presence of ''noncoding, nonexpressed nucleotide sequences'' would affect the exemption status of a PIP at 40 CFR 174.26(a). Commenters argued that because noncoding, nonexpressed sequences are currently excluded from the definition of ''genetic material necessary for the production'' at 40 CFR 174.3, their presence in the recipient plant should not affect the exemption status of a PIP that otherwise meets the exemption criteria.

''Noncoding, nonexpressed nucleotide sequences'' are defined at 40 CFR 174.3, in part as ''nucleotide sequences that are not transcribed and are not involved in gene expression.'' One such example are the left and right border sequences that flank the genetic material that is inserted into the plant genome when using *Agrobacterium*-mediated transformation. These sequences facilitate the integration of the genetic cargo into the plant genome and will remain in the recipient plant together with the genetic material that the developer wishes to express to create the pesticidal trait. Other examples of ''noncoding, nonexpressed nucleotide sequences'' are linker sequences and restriction enzyme recognition sites.

As discussed in the preamble of the proposed rule, ''EPA expects that any ingredients intentionally added during the development of ''PIPs created through genetic engineering from a sexually compatible plant'' that are specific to the production of the active ingredient (*e.g.,* guide RNA, DNA nuclease) and that could function as an inert ingredient would either be transiently transformed or would be removed (*e.g.,* through segregation of the trait) during the breeding process and that if these ingredients have not been removed from the final product the product would not meet the criteria proposed under the new 40 CFR 174.26 and would not qualify for the new exemptions.'' Like the inert ingredients cited in this quote, noncoding, nonexpressed sequences are intentionally added during the development of the PIP to facilitate the integration of the genetic cargo. Thus, EPA finds that if these sequences are not removed from the final product, *i.e.,* the recipient plant, they similarly do not meet the criteria for exemption under 40 CFR 174.26 and 40 CFR 174.27. In this way, the PIPs exempted under this rulemaking remain indistinguishable from those created through conventional breeding.

2. Editing or Insertion of Multiple PIPs in a Single Event

EPA received requests to clarify whether modifications to multiple genes within a single recipient plant would qualify for the exemptions at 40 CFR 174.26. 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. In these instances, 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 (*e.g.,* the M009 PRIA fee is applied three times for the creation of three unique PIPs in a single recipient plant). The exception is a scenario in which the same gene is modified or inserted multiple times across the genome. For example, it may be necessary to modify several homologous genes of a native gene in a recipient plant to create a single PIP (*i.e.,* to create a loss-of-function PIP where the trait requires all homologous genes to be modified). Conversely, a developer may wish to insert multiple copies of the same native gene. 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.

C. PIPs Created Through Genetic Engineering From a Sexually Compatible Plant

1. Identical Substance Criterion

EPA received several comments on the ''identical substance'' criteria stating, amongst other things, that modifications that result in non-identical substances may not result in a change in risk profile and that the requirement for the production of an identical substance is not consistent with the requirements for PIPs from sexually compatible plants that are moved through conventional breeding. In response, EPA has edited the exemption category related to modifications in an existing native gene at 40 CFR 174.26(a)(2) to incorporate the use of polymorphic regions (Unit III.A.2.).

The exemption category at 40 CFR 174.26(a)(2) does not require the production of an identical substance, while still staying within the scope of what could be achieved through conventional breeding and thus within the scope of the proposed rulemaking. The exemption criterion at 40 CFR 174.26(a)(2) now allows for modifications of the existing native gene using a single source plant as a template to match corresponding polymorphic sequence(s) in a native allele of that gene. Polymorphisms are variants of a gene sequence that are shared between native alleles. These genetic variations may be composed of single nucleotides (*i.e.,* SNPs) or larger DNA segments and they are found at the same locus within the genetic sequence of two or more native alleles (Ref. 11). In some cases, enhanced pesticidal properties of a gene product can be attributed to one or more of these genetic variations within a native gene. 40 CFR 174.26(a)(2) allows developers to utilize their knowledge of specific polymorphisms in native alleles to make changes to the native gene in their recipient plant. While this category does not require the entire substance to be identical to a substance found in the sexually compatible population of the recipient plant, it does require the individual polymorphism(s) to have been identified. It is also important to note that this category requires the use of a *single* source plant as a template, meaning it is not allowed to combine polymorphisms from multiple native alleles in a single PIP. By requiring the polymorphic sequences to be identical and the use of a single source plant as a template, this separate exemption category allows the Agency to capture more of the possible genetic variation that can occur in plants, while staying within the bounds of what could have been achieved through conventional breeding.

2. Expression Profile Criterion

EPA proposed at 40 CFR 174.26(b) a criterion that was intended to ensure that the expression profile of exempted PIPs falls within that which is found in the sexually compatible population. Limiting expression profiles of exempted PIPs in this way is a key limitation to prevent novel environmental and dietary exposures. However, commenters expressed concern over the feasibility to generate the information required to demonstrate eligibility for exemption and had several questions on how these requirements could be met (Unit IV.E.4.b.). Additionally, the Agency received requests to clarify whether the criteria that the pesticidal substance may not be expressed at higher levels, in different tissues, or at different developmental stages, would apply simultaneously or independently. Commenters also requested clarification on the identity of the appropriate comparator for the expression profile criteria at 40 CFR 174.26(b). These comments prompted the Agency to reevaluate the text proposed at 40 CFR 174.26(b).

Given the number of comments received surrounding the expression criteria, and that limiting expression profiles of exempted PIPs is a key limitation to prevent novel environmental and dietary exposures, EPA is not codifying proposed 40 CFR 174.26(b) and is instead finalizing specific criteria at codified 40 CFR 174.26(a) related to the types of permissible modifications that may impact expression. EPA now requires that regulatory regions inserted as part of a native gene per codified 40 CFR 174.26(a)(1), be identical to those found in the native gene in the source plant. The exemption category at 40 CFR 174.26(a)(2) specifies that modifications to an existing native gene, which includes regulatory and coding regions, must match corresponding polymorphic sequence(s) in a native allele. By requiring that inserted regulatory regions match those found in the native gene in the source plant and that modified regulatory regions match polymorphic sequences found in a native allele, EPA can ensure that the expression profile of PIPs exempted under 40 CFR 174.26 will stay within the bounds of what could be obtained through conventional breeding. Furthermore, this criterion coupled with the information on the history of safe use (40 CFR 174.95(d)) allows EPA to ensure that the expression profile of PIPs exempt from the requirement of a tolerance under 40 CFR 174.541 meet the requirement that expression be at levels that are not injurious or deleterious to human health.

D. Loss-of-Function PIPs

1. How are Loss-of-Function Traits Regulated Under FIFRA?

EPA received a number of comments questioning whether loss-of-function traits conferring pesticidal effects are considered pesticides under FIFRA. As stated in the preamble of the proposed rule (Ref. 2), EPA considers the modification of existing native genes in a plant that elicit a loss-of-function trait conferring a pesticidal effect, *i.e.,* ''loss-of-function PIPs,'' to be a pesticide. In the case of ''loss-of-function PIPs,'' the genetic material of the plant has been altered to reduce or eliminate the activity of a gene that would otherwise facilitate the susceptibility of that plant to a pathogen; therefore, the reduction or elimination of that activity has a mitigating or pesticidal effect.

FIFRA defines a ''pesticide,'' in relevant part, as ''any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.'' FIFRA section 2(u), 7 U.S.C. 136(u). For ''loss-of-function PIPs'' (now exempted under 40 CFR 174.27), the modified genetic material, *e.g.,* the modified gene or the genetic material surrounding an excised gene, is the pesticidal substance, since that material operates in the plant to mitigate the pest. Further, the modified

genetic material has been modified with the intent to mitigate the pest. Therefore, any plant containing the loss of function trait sold or distributed with pesticidal claims would meet the statutory definition of a pesticide.

Under EPA's regulations, a substance is considered to be intended for a pesticidal purpose if, among other things, the person who distributes or sells the substance as a pesticide product claims, states, or implies that the substance can or should be used as a pesticide; the substance has no significant commercially valuable use other than use for pesticidal purpose; or a person sells or distributes a product with actual or constructive knowledge that the product will be used, or is intended to be used, for a pesticidal purpose. See 40 CFR 152.15. Therefore, products carrying a pesticidal claim, such as stating that the plant variety resists disease, indicate clear pesticidal intent. Further, even if such claims were not made, if the seller or distributor knew that the loss of function trait was contained in the plant, the substance would still be considered to be intended for a pesticidal purpose. Likewise, even for loss-of-function PIPs that result in the complete elimination of activity from the modified genetic material, the intentional modification of the plant's genetic material to result in a pesticidal effect indicates that the developer has actual or constructive knowledge that the substance will be used, or is intended to be used, for a pesticidal purpose and that there is not a significant commercially valuable use other than for a pesticidal purpose. The result is that ''loss-of-function PIPs'' are subject to regulation under FIFRA. This Final Rule exempts ''loss-of-function PIPs'' that meet the criteria under 40 CFR 174.27 from certain regulation under FIFRA. Without this exemption, sale and distribution of plants containing those modifications would require registration under FIFRA.

Furthermore, PIPs from sexually compatible plants have been exempt under 40 CFR 174.25 for over 20 years. Had a developer sought confirmation that their conventionally bred, disease-resistant plant was exempt, EPA would have exempted such a product under 40 CFR 174.25 on the basis that it is a PIP trait that has been created via conventional breeding. (See *e.g.,* 66 FR 37772; July 19, 2001 (FRL–6057–7)). This determination would be made without making a distinction of mode of action (*e.g.,* gene loss-of-function or production of a protein). Disease-resistant traits are often caused by the loss-of-function of a gene, and the 2001 preamble focused on the presence of a pesticidal trait (*i.e.,* disease resistance) and claims of resistance in its determinations that such a trait would be considered a pesticide and a PIP, indicating that EPA did not make a distinction as to whether the disease-resistant trait was conferred via a gene loss-of-function or via production of a proteinaceous substance. Therefore, it is consistent to consider loss-of-function traits to be both pesticides and PIPs.

2. Criteria for the Exemption Specific to ''Loss-of-Function PIPs''

EPA received several comments from industry, trade, and academia on the criterion of substance identity, requesting that the exemptions should be broadened to include non-identical pesticidal substances. By creating a separate exemption for ''loss-of-function PIPs'' with specific criteria and an accompanying definition, EPA finds that ''loss-of-function PIPs'' as described by 40 CFR 174.27 do not require the ''identical substance'' criterion, as do PIPs exempt under 40 CFR 174.26, due to fundamental differences in the pesticidal activity of ''loss-of-function PIPs'' compared to PIPs exempt under 40 CFR 174.26.

''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). Mutations that lead to a loss of gene function occur naturally and are prevalent within many organisms, including plants. For example, one study of 1,071 genomes of the model plant *Arabidopsis thaliana* showed a total of 60,819 loss-of-function variants within 12,907 genes, out of a genome-wide total of approximately 25,500 genes (Refs. 12, 13). In addition to their natural occurrence as a result of various biotic and abiotic factors, plant breeders have intentionally induced these types of mutations during the conventional breeding process. One example is the treatment of seeds by chemical mutagens, which is a technique used by breeders to create new plant varieties (Refs. 14, 15).

The traits that may result from the loss of function of a gene are diverse, ranging from altered grain size, increased drought tolerance, and resistance to plant diseases (Refs. 16–20). Disease resistance in plants from the loss of function of S-genes (susceptibility genes) have been identified in natural plant populations, and researchers have used knowledge about naturally occurring gene variants to create pest resistance in various plant species using genetic engineering (Refs. 18, 19). For example, genetically engineered deletions in parts of the regulatory region of the SWEET14 gene in rice created a plant line that is resistant to the *Xanthomonas oryzae* pv. oryzae (*Xoo*) pathogen, and genetically engineered loss-of-function of eIF4E achieved potyvirus resistance in cucumber (Refs. 21, 22).

As previously stated, EPA does not require an ''identical substance'' criterion for ''loss-of-function PIPs,'' and this is because mutations in any part of a gene have the potential to result in the loss of its function. Examples include deletions within the regulatory region that lead to the reduced expression (and thus reduced abundance) of an unmodified protein, or a single nucleotide change in the coding region, which can result in the creation of a premature stop codon, leading to the production of a shorter version of the protein originally encoded by that gene. Other changes to the coding region may also lead to mis-splicing of the pre-mRNA, which can subsequently result in the degradation of the pre-mRNA (no protein produced) or the production of a non-functional protein (Refs. 23, 24). If a non-functional protein is produced, a normal part of routine biological processes is for the cell to recognize it as such and target it for degradation into its amino acid constituents. This turnover of protein occurs independent of how the non-functional protein was created, be it the result from a permanent genetic change (either through natural or induced mutation) or errors created when cells transcribe and/or translate the genetic code (Refs. 25–28). The ability of the cell to recognize and break down non-functional proteins is a routine cell function, and it enables the organism to be economical with its resources by reusing the amino acids for those proteins that do serve a purpose.

Based on the prevalence of loss-of-function mutations in plants and the biological considerations of protein homeostasis, EPA finds that it does not need the same requirements on characteristics as it does for ''PIPs created through genetic engineering from a sexually compatible plant.'' Therefore, ''loss-of-function PIPs,'' as exempted under 40 CFR 174.27, are still supported by the risk assessment as presented in the proposed rule.

As the ''loss-of-function PIP'' exemption is focused on function, there is no nucleic acid sequence requirement in the exemption criteria under 40 CFR 174.27 or in the exemption documentation under 40 CFR 174.96. Commenters have stated a concern that

minor crops may face a disadvantage due to fewer genomic resources being available for their specific crop species. For example, one commenter stated that knowledge of genes in major crops or model organisms can inform the development of minor crops due to conserved gene function from a shared common ancestor, even when those plants are no longer sexually compatible. EPA believes that the codified exemption for ''loss-of-function PIPs'' with its focus on function will allow for use of this knowledge and provide a benefit for developers, including those of minor crops.

E. Eligibility Determination Process

1. Options To Determine Exemption Eligibility

In the proposal, all exempted ''PIPs created through genetic engineering from a sexually compatible plant'' had the option of self-determination. However, in the final rule, only developers of ''loss-of-function PIPs'' (40 CFR 174.27) have the option to self-determine whether the exemption criteria are met.

The Agency finds the approach to require an EPA confirmation for ''PIPs created through genetic engineering from sexually compatible plants'' justified. Commenters felt that a mandatory EPA confirmation process would prevent an incorrect exemption determination. EPA agrees with commenters arguing that doing so will provide additional clarity to developers of ''PIPs created through genetic engineering from sexually compatible plants'' and increase transparency and public trust in products containing these PIPs.

Other commenters were supportive of the flexibility that a mandatory self-determination process with a voluntary EPA confirmation process would provide. EPA acknowledges the value of this flexibility and has determined that developers of ''loss-of-function PIPs'' will have the option to either self-determine or request EPA confirmation of exemption eligibility. Given the straightforward nature of the criteria describing ''loss-of-function PIPs'' (*i.e.,* a focus on function rather than source plant or underlying sequence), EPA believes it appropriate for ''loss-of-function PIPs'' to be eligible for the self-determination option as it is unlikely for a developer to accidentally mis-determine these PIPs. Furthermore, the mode of action of ''loss-of-function PIPs'' (*i.e.,* reduction or elimination of an endogenous gene) is fundamentally different from ''PIPs created through genetic engineering from a sexually compatible plant'' (*e.g.,* intentional production of a pesticidal protein), and as such, further lends itself to the availability of a self-determination option.

2. Extension of Exemption Status

Commenters were largely supportive of the option to transfer the exemption status of a particular PIP to other plant varieties. Regarding this option, one commenter felt that the criterion in the proposal at 40 CFR 174.90(e)(1)(ii) that required that the same phenotype be created through non-homologous end joining repair modifications was too narrow. EPA agreed with this comment and, given the creation of a separate exemption for ''loss-of-function PIPs'' focused on function, was able to revise the exemption extension criteria for ''loss-of-function PIPs'' to be similarly focused on function (Unit III.C.1.).

3. Contents of a Self-Determination Letter

In the proposal, EPA proposed to require submitters of self-determination letters to identify the PIP (at proposed 40 CFR 174.91(b)(2) and 40 CFR 174.91(b)(3)). Two commenters stated that EPA should require additional information on the PIP with the submission of a self-determination letter. Specifically, it was requested that EPA require information on the plant species, a description of the pesticidal trait, and a short summary of how the pesticidal trait was introduced into the plant variety. It was also requested that EPA require developers to submit information that would be required for an EPA confirmation. EPA agrees that information on the recipient plant species and a unique gene identifier should be included in the self-determination letter and has updated the text at 40 CFR 174.91 to reflect this (Unit III.C.2.). Because the identity of the PIP may or may not include the name of the modified gene or plant species (*e.g.,* the identity of the PIP could also be a trade name), the Agency has clarified that a gene identifier and the identity of the recipient plant must also be included in the submission of a self-determination letter.

Regarding the other suggestions, such as a description of the pesticidal trait, a short summary of how the trait was introduced, and other information otherwise provided to the Agency as part of the EPA confirmation process, the Agency does not find this information necessary to be submitted with the self-determination letter. This is because the self-determination process does not involve an EPA review or confirmation. However, the information provided during an EPA confirmation is the same information required to be maintained by the recordkeeping requirements under 40 CFR 174.73, which equally applies to those submitting a self-determination of exemption. As part of the recordkeeping requirements, the information suggested by the commenters must already be made available to EPA upon request. Although the Agency is not requiring a summary description of the pesticidal trait and how it was introduced in the self-determination letter, the Agency agrees that identifying the trait type (*e.g.,* insect resistance or disease resistance) would provide useful information for the public and for State level agencies and edited 40 CFR 174.91(b)(2) to reflect this. Thus, the language at 40 CFR 174.91(b)(2) now requires information on plant species, gene identifier, and trait type.

4. Documentation for an Exemption for ''PIPs Created Through Genetic Engineering From a Sexually Compatible Plant''

a. Scope of the Required Documentation

EPA received comments on the scope of the documentation that is required to be produced to support an exemption for ''PIPs created through genetic engineering from a sexually compatible plant.'' One commenter requested that, in addition to discussing the categories of information needed to assess applicability of the exemption to a PIP, EPA furthermore establish expectations in the regulatory text on what information the Agency deems sufficient to satisfy each of the exemption criteria. In line with this, one commenter suggested to revise 40 CFR 174.95(a)(2) to replace ''information to demonstrate the recipient plant and the source plant are sexually compatible'' with ''information to support that the recipient plant and the source plant are sexually compatible.'' The Agency agrees with this suggestion as a developer may, for example, provide a peer-reviewed literature rationale instead of generating empirical data to demonstrate that two plants are sexually compatible. The Agency revised the regulatory text in the final rule accordingly (Unit III.C.4.a.).

The same commenter also suggested two revisions to 40 CFR 174.95(c)(1). First, the commenter suggested that the documentation requirements should limit sequence comparison to nucleic acids, rather than require both the nucleic acid and the amino acid sequence for proteinaceous PIPs and to limit the nucleic acid sequence comparison to the location of the

intended modification(s) rather than the entire PIP. Second, the commenter requested that if an amino acid sequence was required, EPA further clarify the language on the sequence requirements to state ''nucleotide sequence and deduced amino acid sequence.'' EPA has revised the text at 40 CFR 174.95(c)(1) for increased clarity as to the required sequence information based on the relevant comparator, *i.e.,* the specific comparator at 40 CFR 174.95(c) is now listed based on the corresponding exemption category at 40 CFR 174.26. The Agency maintains that the entire nucleic acid sequence must be provided for all PIPs exempted under 174.26(a), as both exemptions at 40 CFR 174.26(a) allow for modifications in the regulatory regions. Thus, providing EPA with the nucleic acid sequence of the entire gene will allow the determination if the modifications meet the exemption requirements (Unit III.C.4.a.). The Agency maintains that the full-length amino acid sequence must additionally be provided for proteinaceous PIPs but agrees with the commenter that the deduced amino acid sequence would be sufficient to inform the identity of that PIP in these instances.

Commenters requested that EPA exclude wild relatives as potential source plants and/or impose geographic restrictions on source plants, noting that non-target organisms living within the range of the wild donor plants would have adapted to exposures from these wild plants and that non-target organisms from outside this range may therefore be negatively impacted by a PIP from the wild plant due to lack of previous exposure. Additionally, it was noted that allowing sexually compatible wild relatives as source plants may result in toxins from these plants being missed as part of the plant breeder screening.

EPA understands that wild relatives provide an important source of genetic variation for developers and therefore has chosen not to exclude them from use as sexually compatible source plants for exempt PIPs. However, to address the concern raised by the commenters, EPA has added a requirement at 40 CFR 174.95(d)(2) that if the source plant is a wild relative of the recipient plant, the developer must describe why the PIP is not anticipated to pose a hazard to humans or the environment. EPA provides a list in the regulatory text at 40 CFR 174.95(d)(2) of the types of information that can be used to describe why a PIP is not anticipated to pose a hazard to humans or the environment.

b. Feasibility To Meet the PIP Expression Criteria and Develop Adequate Documentation

EPA received several comments on the proposed rule regarding the PIP expression criteria at 40 CFR 174.26(b) and the associated documentation requirements at 40 CFR 174.95(c)(2). Several commenters raised concerns that meeting the documentation requirements would be impractical and cost prohibitive given the large variation in plant gene expression between tissues and growth stages, especially when considering gene expression in different environmental conditions. One commenter submitted that data to meet the expression limitation exemption criteria should only be required if the intent of the modification is to increase levels of the expressed pesticidal substance. This approach is consistent with the Agency's analysis of gene expression articulated in the proposal. Specifically, EPA found that although variations in the production of plant substances will occur in response to environmental conditions, there are physiological and practical considerations that limit the expression level, and thus the abundance of a particular substance in plants that are sexually compatible. EPA finds that this is especially true for regulatory regions and polymorphic sequences that are present in regulatory regions that are moved between native alleles. In other words, there is the expectation that the expression pattern of a PIP would be within that what is found within the sexually compatible population, so long as it is under the control of the regulatory elements found within a native allele.

Consistent with this assessment and taking into consideration the comments received on the impracticality and potential financial burden of determining the expression levels to comply with proposed 40 CFR 174.95(c)(2), the Agency removed the exemption criterion at proposed 40 CFR 174.26(a)(2)(i) that would have allowed modifications to regulatory regions for the purpose of altering the expression level of a pesticidal substance. Instead, EPA is now requiring at 40 CFR 174.26(a)(1) that any regulatory region that is inserted as part of a native gene must be identical in nucleotide sequence to the regulatory region of the native gene as it is identified in the source plant. Similarly, 40 CFR 174.26(a)(2) allows regulatory region changes only based on polymorphic sequence(s) identified in a native allele of the modified gene. In making these revisions to 40 CFR 174.26, EPA is able to remove the requirements for expression profile confirmation at proposed 40 CFR 174.95(c)(2), as the expectation is that the expression profiles of PIPs that meet these exemption criteria at 40 CFR 174.26(a) will not be outside of that what is found within the sexually compatible population of the recipient plant.

5. Activities That Require Submission of an Eligibility Determination

Two commenters requested clarification on which activities may require a separate notification of self-determination for a PIP under 40 CFR 174.541. Specifically, commenters requested clarification in those instances in which a plant containing the PIP is imported to the United States for the distribution in commerce for consumption or planting in the absence of a tolerance or tolerance exemption granted under FFDCA.

EPA is confirming that the Agency is requiring a separate eligibility determination under 40 CFR 174.541 for residues of those PIPs that are imported into the United States and that are used for food or feed if the developer has not already obtained an exemption under 40 CFR 174.21. As discussed in the preamble of the proposed rule, a separate submission of the eligibility determination of the FFDCA exemption for a PIP proposed for use in food or feed is required only if it has not already been submitted under FIFRA. To clarify, EPA has added a new paragraph (g) to 40 CFR 174.90, which explains that a duplicative eligibility submission is not required for purposes of 40 CFR 174.541(c), if it is already being submitted for purposes of 40 CFR 174.21(d). The proposal discussed one such scenario where this might be the case (*e.g.,* Unit VI.C.1. of the proposed rule). Briefly, a developer will need an exemption eligibility determination for the purposes of FFDCA but not FIFRA when residues of a PIP will be in or on food imported into the United States, but the PIP is not intended to be sold or distributed for pesticidal use (*e.g.,* PIP containing seed or plant sold for planting) in the United States. In that case, the PIP residues in the imported food would need a tolerance or tolerance exemption to allow for distribution in interstate commerce in the United States under the FFDCA, but would not need a FIFRA exemption since it is not intended to be sold or distributed for pesticidal purposes in the United States.

Other commenters inquired whether testing of PIPs at or under 10 acres of land would require an Experimental Use Permit (EUP) under FIFRA section 5 and

therefore whether an eligibility determination for certain PIPs would be required at these acreages. 40 CFR 172.3 applies to PIPs. As described in 40 CFR 172.3, tests on 10 acres or less are presumed to not require an EUP so long as any food or feed crops involved in, or affected by, such tests (including, but not limited to, crops subsequently grown on such land which may reasonably be expected to contain residues of the tested pesticides) are destroyed or consumed only by experimental animals unless an appropriate tolerance or exemption from a tolerance has been established under FFDCA for residues of the pesticide. Further, pursuant to 40 CFR 172.3(e), EPA may, on a case-by-case basis, require that testing be carried out under an EUP even if such testing involves 10 acres or less. For a PIP subject to this rulemaking that would be used in testing taking place on 10 acres or less to be able to take advantage of the presumption in 40 CFR 172.3, that PIP would need to either demonstrate that the appropriate tolerance or exemption has been established or follow the requirements of crop destruction. Pursuant to subpart E of 40 CFR 174 as codified in this rule, for PIPs exempted under 40 CFR 174.26, demonstrating that the tolerance exemption at section 40 CFR 174.541 applied would require an EPA confirmation, and for PIPs exempted under 40 CFR 174.27, it would require the submission of a self-determination. For a PIP for which a tolerance exemption has not been established, in addition to requirements of crop destruction for field testing at or under 10 acres, EPA previously published and still relies on guidance (Ref. 29) detailing containment measures to restrict the flow of genetic material, including seeds, from field tests to minimize the potential for PIP residues that do not have a tolerance exemption to enter the food supply. These additional considerations are crucial to prevent PIPs lacking a tolerance exemption from entering the food supply and the consequences of adulteration under FFDCA. EPA notes that it is expecting to provide an update to the information and/or process provided in PRN 2007–2 (Ref. 29) regarding measures needed for containing small-scale testing of PIPs in light of changes in regulatory oversight due to USDA's recently revised 7 CFR part 340 regulations.

6. Submitting Confidential Business Information (CBI)

Several commenters noted that information included in a request for EPA confirmation may be classified as CBI and requested assurance and clarification for how EPA would protect intellectual property and other proprietary information. As EPA is using its existing electronic reporting site for receiving submissions, this information will be transmitted to EPA in a secure manner. As stated in 40 CFR 174.90(c), any claims of confidentiality for information submitted in the request for EPA confirmation must be made in accordance with the procedures outlined in 40 CFR 174.9 of subpart A. 40 CFR 174.9 instructs a submitter on how to claim data or other information as CBI. Information likely to be claimed as CBI may be part of the documentation for an exemption (*e.g.,* sequence information on the pesticidal substance). Developers also have the option to claim information submitted as part of the self-determination as CBI (*e.g.,* gene ID, plant species). However, it is important to note that every individual piece of information claimed as CBI must be supported by its own substantiation. For this reason, and for reasons of public transparency, as it has for all PIPs, EPA continues to encourage PIP developers to limit their claims to CBI to only the most pertinent pieces of information.

F. Endangered Species Assessment

EPA received public comment regarding whether the proposed exemption may affect endangered species. EPA determined that this action invokes obligations under the Endangered Species Act because this is a discretionary action that exempts certain pesticidal substances from some requirements under FIFRA, such that the exemptions could cause potential exposures in the environment. Therefore, EPA conducted an Endangered Species Assessment for ''PIPs created through genetic engineering from a sexually compatible plant'' and for ''loss-of-function PIPs.''

In the proposed rule, after careful consideration of potential interactions that the PIPs proposed for exemption may have with nontarget organisms (see Unit VI.A.3. of the proposed rule), EPA preliminarily determined that use of the PIPs proposed for exemption is not likely to cause unreasonable adverse effects on the environment and humans in the absence of regulatory oversight (although ''regulatory oversight'' still exists in the form of the adverse effects reporting requirement in existing 40 CFR 174.71) resulting in a reasonable expectation that no discernible effects to nontarget organisms will occur. As no discernible effects to nontarget organisms are reasonably expected to occur due to the use of these PIPs, which necessarily includes any threatened or endangered species (listed species), EPA therefore reaches a ''No Effect'' determination for listed species and their critical habitats.

Herein, EPA provides brief summaries of key considerations used in the Agency's determination that the PIP exemptions proposed in the 2020 preamble and finalized in this rule are reasonably expected to result in no discernable effects to nontarget organisms, including listed species. In the proposed rule, EPA considered several factors in determining whether PIPs that meet the criteria under proposed 40 CFR 174.26 could be exempted from FIFRA requirements in order to meet the 40 CFR 174.21(a) requirement (Unit VI.A.3.h. of the proposed rule). In its assessment, the Agency relied on the large body of knowledge that currently exists on sexually compatible plants and genetic diversity. Briefly, with regard to the potential ecological effects, the Agency found that there is: ''(1) Low potential for novel exposures; (2) Low potential for levels of ''PIPs created through genetic engineering from a sexually compatible plant'' to exceed levels found in sexually compatible plants; and (3) Low potential for ''PIPs created through genetic engineering from a sexually compatible plant'' to move from cultivated plants to wild or weedy relatives through gene flow and increase weediness.'' (Unit VI.A.3. of the proposed rule). EPA also evaluated considerations specific to newer biotechnology techniques related to the PIPs proposed for exemption and found that their use in creating these PIPs would pose negligible risk to the environment. Lastly, the Agency found that the likelihood is negligible that the transfer of a PIP via biotechnology from a nonagricultural (wild) relative to an agricultural one would pose a greater risk than if it were transferred through conventional breeding.

In summary, PIPs that are exempted under 40 CFR 174.26 represent a subset of substances already present in related plants and are equivalent both in identity and in expression profile (how much, where, and when the substances are expressed in plants). As ''loss-of-function PIPs'' exempted under 40 CFR 174.27 were originally proposed as a subcategory of PIPs exempted under 40 CFR 174.26, they too fall within the scope of the Agency's analysis in the proposed rule preamble. Pesticidal traits resulting from the loss-of-function of an endogenous gene are common occurrences in wild plants and in conventional breeding (Refs. 18, 19) and EPA finds that there is no potential for

novel exposures or hazards for ''loss-of-function PIPs,'' as this group of PIPs is characterized by a modification that leads to the reduction or elimination of the activity of a gene that had already been present in the recipient plant. As the PIPs exempted under this rule are considered to be equivalent to those already found in nature and used in conventional breeding, there is a reasonable expectation that no discernible effects to listed species will occur from their use. As no discernible effects are reasonably expected to occur to listed species due to the use of these PIPs, EPA therefore reaches a ''No Effect'' determination for listed species and their critical habitats.

VII. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

1. Response to Comments to the Proposed Rule to Exempt Certain Plant-Incorporated Protectants (PIPs) Derived from Newer Technologies. Available at *https://www.regulations.gov* under Docket ID No. EPA–HQ–OPP–2019–0508.
2. USEPA. 2020. Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived from Newer Technologies. 85 FR 64308, October 9, 2020 (FRL–10014–10). Available at *https://www.regulations.gov* under Docket ID No. EPA–HQ–OPP–2019–0508.
3. USEPA, USFDA, and USDA. Modernizing the Regulatory System for Biotechnology Products: Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology. 2017; Available from: *https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/update-coordinated-framework-regulation-biotechnology.*
4. USEPA. 2022. Cost Analysis For the Final Rule Exempting Certain Plant-Incorporated Protectants (PIPs) from Registration. Available at *https://www.regulations.gov* under Docket ID No. EPA–HQ–OPP–2019–0508.
5. Mhoswa L., O'Neill M.M., Mphahlele M.M., Oates C.N., Payn K.G., Slippers B., Myburg A.A., and Naidoo S. *A Genome-Wide Association Study for Resistance to the Insect Pest Leptocybe invasa in Eucalyptus grandis Reveals Genomic Regions and Positional Candidate Defense Genes.* Plant and Cell Physiology. 2020. 61(7), pp.1285–96.
6. Jamie, Gabriel A., and Joana I. Meier. *The persistence of polymorphisms across species radiations.* Trends in Ecology & Evolution. 2020. 35(9), pp.795–808.
7. Pesticide Registration (PR) Notice 2011–3. Standard Format for Data Submitted Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Certain Provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), November 2011. Available online at *https://www.epa.gov/sites/default/files/2014-04/documents/pr2011-3.pdf.*
8. USEPA **Federal Register**. 2001. Regulation Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants (Formerly Plant-Pesticides). 66 FR 37772, July 19, 2001 (FRL–6057–7). Available online at *https://archive.epa.gov/pesticides/biopesticides/web/pdf/pip_rule.pdf.*
9. Kaiser, N., Douches, D., Dhingra, A., Glenn, K.C., Herzig, P.R., Stowe, E.C., and Swarup, S. *The role of conventional plant breeding in ensuring safe levels of naturally occuring toxins in food crops.* Trends in Food Science & Technology. 2020. 100, pp.51–66.
10. Graham, N., Patil, G.B., Bubeck, D.M., Dobert, R.C., Glenn, K.C., Gutsche, A.T., Kumar, S., Lindbo, J.A., Maas, L., May, G.D. and Vega-Sanchez, M.E. *Plant genome editing and the relevance of off-target changes.* Plant Physiology. 2020. 183(4), pp.1453–1471.
11. Hartl, D.L., *A primer of population genetics.* 3rd ed. 2000, Sunderland, MA: Sinauer Associates, Inc.
12. Xu, Y.C., Niu, X.M., Li, X.X., He, W., Chen, J.F., Zou, Y.P., Wu, Q., Zhang, Y.E., Busch, W. and Guo, Y.L., 2019. *Adaptation and phenotypic diversification in Arabidopsis through loss-of-function mutations in protein-coding genes.* The Plant Cell, 31(5), pp.1012–1025.
13. Kaul, S., Koo, H.L., Jenkins, J., Rizzo, M., Rooney, T., Tallon, L.J., Feldblyum, T., Nierman, W., Benito, M.I., Lin, X. and Town, C.D., 2000. *Analysis of the genome sequence of the flowering plant* Arabidopsis thaliana. Nature, 408(6814), pp.796–815.
14. Oladosu, Y., Rafii, M.Y., Abdullah, N., Hussin, G., Ramli, A., Rahim, H.A., Miah, G. and Usman, M., 2016. *Principle and application of plant mutagenesis in crop improvement: a review.* Biotechnology & Biotechnological Equipment, 30(1), pp.1–16.
15. Jankowicz-Cieslak, J., Mba, C. and Till, B.J., 2017. *Mutagenesis for crop breeding and functional genomics.* In Biotechnologies for plant mutation breeding (pp.3–18). Springer, Cham.
16. Duan, P., Xu, J., Zeng, D., Zhang, B., Geng, M., Zhang, G., Huang, K., Huang, L., Xu, R., Ge, S. and Qian, Q., 2017. *Natural variation in the promoter of GSE5 contributes to grain size diversity in rice.* Molecular plant, 10(5), pp.685–694.
17. Monroe, J.G., Powell, T., Price, N., Mullen, J.L., Howard, A., Evans, K., Lovell, J.T. and McKay, J.K., 2018. *Drought adaptation in Arabidopsis thaliana by extensive genetic loss-of-function.* Elife, 7.
18. Bai, Y., Pavan, S., Zheng, Z., Zappel, N.F., Reinstädler, A., Lotti, C., De Giovanni, C., Ricciardi, L., Lindhout, P., Visser, R. and Theres, K., 2008. *Naturally occurring broad-spectrum powdery mildew resistance in a Central American tomato accession is caused by loss of Mlo function.* Molecular Plant-Microbe Interactions, 21(1), pp.30–39.
19. Acevedo-Garcia, J., Kusch, S. and Panstruga, R., 2014. *Magical mystery tour: MLO proteins in plant immunity and beyond.* New Phytologist, 204(2), pp.273–281.
20. Van de Wiel, C.C.M., Schaart, J.G., Lotz, L.A.P. and Smulders, M.J.M. *New traits in crops produced by genome editing techniques based on deletions.* Plant biotechnology reports. 2017. 11(1), pp.1–8.
21. Li, T., Liu, B., Spalding, M.H., Weeks, D.P. and Yang, B., 2012. *High-efficiency TALEN-based gene editing produces disease-resistant rice.* Nature biotechnology, 30(5), pp.390–392.
22. Chandrasekaran, J., Brumin, M., Wolf, D., Leibman, D., Klap, C., Pearlsman, M., Sherman, A., Arazi, T. and Gal-On, A., 2016. *Development of broad virus resistance in non-transgenic cucumber using CRISPR/Cas9 technology.* Molecular plant pathology, 17(7), pp.1140–1153.
23. Reddy A.S.N., Marquez Y., Kalyna M., and Barta A. *Complexity of the alternative splicing landscape in plants.* The Plant Cell. 2013. 25(10), pp.3657–83.
24. Roy SW, Irimia M. *Intron mis-splicing: no alternative?.* Genome biology. 2008. 9(2), pp.1–3.
25. Merchante, C., Stepanova A. N., and Alonso J. M. *Translation regulation in plants: an interesting past, an exciting present and a promising future.* The Plant Journal. 2017. 90, pp. 628–653.
26. Gordon A.J., Satory D., Halliday J.A., and Herman C. *Lost in transcription: transient errors in information transfer.* Current opinion in microbiology. 2015. 24, pp.80–7.
27. Li L., Nelson C.J., Trösch J., Castleden I., and Huang S., Millar A.H. *Protein degradation rate in Arabidopsis thaliana leaf growth and development.* The Plant Cell. 2017. 29(2), pp.207–28.
28. Toyama B.H. and Hetzer M.W. *Protein homeostasis: live long, won't prosper.* Nature reviews Molecular cell biology. 2013. 14(1), pp.55–61.
29. Pesticide Registration (PR) Notice 2007–2: Guidance on Small-Scale Field Testing and Low-level Presence in Food of Plant-incorporated Protectants (PIPs), April 30, 2007. Available online at *https://www.epa.gov/pesticide-registration/prn-2007-2-guidance-small-scale-field-testing-and-low-level-presence-food.*
30. USEPA. Supporting Statement for the Information Collection Request (ICR) entitled: *Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived from Newer Technologies Rulemaking (Final Rule; RIN 2070–AK54).* EPA ICR No.: 2619.02; OMB Control No. 2070–0214. (May 2023).

VIII. FIFRA Review Requirements

Pursuant to FIFRA section 25(a), EPA submitted the draft final rule to the United States Department of Agriculture (USDA) for review, with a copy sent to the appropriate Congressional Committees as required under FIFRA section 25(a). The Agency did not receive any comments from USDA.

In accordance with FIFRA section 25(d), the EPA asked the FIFRA Scientific Advisory Panel (SAP) to waive review of the draft final rule, as was done for the draft proposed rule. The FIFRA SAP waived its scientific review of the draft final rule on October 12, 2022, because the rule does not raise scientific or science policy issues that warrant a scientific review by the SAP.

IX. Statutory and Executive Order Reviews

Additional information about these statutes and Executive Orders can be found at *https://www.epa.gov/laws-regulations/laws-and-executive-orders.*

A. Executive Orders 12866: Regulatory Planning and Review and 14094: Modernizing Regulatory Review

This action is a significant regulatory action that was submitted to the Office of Management and Budget (OMB) for review under Executive Order 12866 (58 FR 51735, October 4, 1993), as amended by Executive Order 14094 (88 FR 21879, April 11, 2023). Any changes made in response to OMB recommendations during that review have been documented in the docket. EPA prepared an analysis of the potential costs and benefits associated with this action (Ref. 4) which is summarized in more detail in Unit I.E., and included in the docket.

B. Paperwork Reduction Act (PRA)

The information collection activities in this rule have been submitted for approval to OMB under the PRA, 44 U.S.C. 3501 *et seq.* The Information Collection Request (ICR) document that EPA prepared is assigned EPA ICR No. 2619.02 (Ref. 30), and identified by OMB Control No. 2070–0214. You can find a copy of the ICR in the docket for this rule, and it is briefly summarized here. The information collection requirements are not enforceable until OMB approves them.

The information collection activities in this rule are associated with the exemption eligibility process (*i.e.,* self-determination, request for EPA confirmation, and associated recordkeeping) established in this rule as an alternative to the existing pesticide registration and tolerance activities that are currently approved by OMB under OMB Control No. 2070–0060 (EPA ICR No. 0277.23), OMB Control No. 2070–0142 (EPA ICR No. 1693.10), OMB Control No. 2070–0028 (EPA ICR No. 0143.13, and OMB Control No. 2070–0024 (EPA ICR No. 0597.13). Once this ICR is approved, EPA intends to amend the ICR approved by OMB under OMB Control No. 2070–0060 (EPA ICR No. 0277.23) to incorporate the information collection activities and burden attributable to this rule.

Respondents/affected entities: See Unit I.A.

Respondent's obligation to respond: Required to obtain the exemption (40 CFR part 174).

Frequency of response: On occasion.

Total estimated number of respondents: 10.

Total estimated number of responses: 10 (per year), which reflects an estimate of 1 response per respondent each year. The ICR accounts for the most conservative burden estimate, which the Agency projects will be up to 10 submissions per year.

Total estimated burden: 850 hours (per year), which reflects an approximate burden of 85 hours per submission. Burden is defined at 5 CFR 1320.3(b).

Total estimated cost: $125,800 (per year), includes $0 annualized capital or operation and maintenance costs.

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in 40 CFR are listed in 40 CFR part 9. When OMB approves this ICR, the Agency will announce that approval in the **Federal Register** and publish a technical amendment to 40 CFR part 9 to display the OMB control number for the approved information collection activities contained in this final rule.

C. Regulatory Flexibility Act (RFA)

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA, 5 U.S.C. 601 *et seq.* In making this determination, EPA concludes that the impact of concern for this rule is any significant adverse economic impact on small entities and that the Agency is certifying that this rule will not have a significant economic impact on a substantial number of small entities because the rule relieves regulatory burden on the small entities subject to the rule. The rule is expected to reduce costs to developers of ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs,'' and the cost savings per product are approximately $472,000–$886,000. The cost savings per product will be realized when the developer submits a letter of self-determination or requests EPA confirmation, as applicable. The exemption for ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs'' reduces the costs associated with meeting regulatory requirements for these types of PIPs and therefore removes a potential barrier to market entry for small entities. Of the entities likely to develop PIPs that meet the exemptions outlined in this rulemaking, EPA currently estimates that approximately 80% are small entities.

I have therefore concluded that this action will relieve regulatory burden for all directly regulated small entities. The basis for this determination is presented in the small entity analysis prepared as part of the cost analysis for this rulemaking (Ref. 4), which is summarized in Unit I.E., and a copy is available in the docket.

D. Unfunded Mandates Reform Act (UMRA)

This action does not contain an unfunded mandate of $100 million or more as described in UMRA, 2 U.S.C. 1531–1538, and does not significantly or uniquely affect small governments. This action is not expected to impose an enforceable duty on any State, local or Tribal governments, and the requirements imposed on the private sector are not expected to result in annual expenditures of $100 million or more. Accordingly, EPA has determined that the requirements of sections 202, 203, or 205 do not apply to this action.

E. Executive Order 13132: Federalism

This action does not have federalism implications as specified in Executive Order 13132 (64 FR 43255, August 10, 1999), because it will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Thus, Executive Order 13132 does not apply to this action.

F. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments

This action does not have Tribal implications as specified in Executive Order 13175 (65 FR 67249, November 9, 2000), because it will not have substantial direct effects on Tribal governments, on the relationship

between the Federal Government and the Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Thus, Executive Order 13175 does not apply to this action.

G. Executive Order 13045: Protection of Children From Environmental Health Risks and Safety Risks

EPA interprets Executive Order 13045 (62 FR 19885, April 23, 1997) as applying to those regulatory actions that concern environmental health or safety risks that the EPA has reason to believe may disproportionately affect children, per the definition of ''covered regulatory action'' in section 2–202 of the Executive Order. This action is not subject to Executive Order 13045 because it does not concern an environmental health risk or safety risk.

H. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution or Use

This action is not a ''significant energy action'' as defined in Executive Order 13211 (66 FR 28355, May 22, 2001), because it is not likely to have a significant adverse effect on the supply, distribution or use of energy and has not otherwise been designated as a significant energy action by the Administrator of the Office of Information and Regulatory Affairs.

I. National Technology Transfer Advancement Act (NTTAA)

This action does not involve technical standards that would require Agency consideration under NTTAA section 12(d), 15 U.S.C. 272.

J. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations and Low-Income Populations

Executive Order 12898 (59 FR 7629, February 16, 1994) directs Federal agencies, to the greatest extent practicable and permitted by law, to make environmental justice part of their mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of their programs, policies, and activities on minority populations (people of color and/or indigenous peoples) and low-income populations.

EPA believes that this type of action does not concern human health or environmental conditions and therefore cannot be evaluated with respect to potentially disproportionate and adverse effects on people of color, low-income populations and/or indigenous peoples. Although this action does not concern human health or environmental conditions, EPA considered potential environmental justice concerns during the development of the proposed rule, sought comments specifically on this point with regard to the proposed exemptions, and finds that this action will not result in disproportionately high and adverse human health, environmental, climate-related, or other cumulative impacts on disadvantaged communities.

K. Congressional Review Act (CRA)

This action is subject to the CRA, 5 U.S.C. 801 *et seq.,* and EPA will submit a rule report to each House of the Congress and to the Comptroller General of the United States. This action is not a ''major rule'' as defined by 5 U.S.C. 804(2).

L. Executive Orders 13874: Modernizing the Regulatory Framework for Agricultural Biotechnology Products and 14801: Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy

This action is intended to further implement section 4(b) of Executive Order 13874 (84 FR 27899, June 11, 2019), and section 8 of Executive Order 14801 (87 FR 56849, September 12, 2022). This final rule may promote future innovation and competitiveness by efficiently exempting through regulation qualifying ''PIPs created through genetic engineering from a sexually compatible plant'' and ''loss-of-function PIPs'' that meet the FIFRA and FFDCA standards for exemption.

List of Subjects in 40 CFR Part 174

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Plant-incorporated protectants, Reporting and recordkeeping requirements.

Michael S. Regan,
Administrator.

Therefore, for the reasons stated in the preamble, 40 CFR part 174 is amended as follows:

PART 174—PROCEDURES AND REQUIREMENTS FOR PLANT-INCORPORATED PROTECTANTS

■ 1. The authority citation for part 174 continues to read as follows:

Authority: 7 U.S.C. 136–136y; 21 U.S.C. 321(q), 346a and 371.

■ 2. Amend § 174.3 by adding in alphabetical order definitions for ''Gene'', ''Genetic engineering'', ''Loss-of-function plant-incorporated protectant'', ''Native allele'', and ''Native gene'' and revising the definition of ''Sexually compatible'' to read as follows:

§ 174.3 Definitions.

* * * * *

Gene, and other grammatical variants such as ''genic,'' means a unit of heritable genetic material that is comprised of the genetic material necessary for the production of a substance.

Genetic engineering means the modification of the genome of an organism using recombinant, synthesized, or amplified nucleic acids or other techniques excluded from the definition of conventional breeding.

* * * * *

Loss-of-function plant-incorporated protectant means a plant-incorporated protectant in which the genetic material of a native gene is modified to result in a pesticidal effect through the reduction or elimination of the activity of that gene. For purposes of loss-of-function plant-incorporated protectants, the active ingredient and pesticidal substance are one and the same and are defined as the genetic material that has been modified to create the pesticidal trait (*i.e.,* modification of the sequence of nucleic acids). Loss-of-function plant-incorporated protectants do not include instances where the reduction or elimination of the activity of the modified native gene results in the intentional increase of activity of another pesticidal gene.

Native allele means a variant of a native gene that is identified in the genetic diversity of plants sexually compatible with the recipient plant.

Native gene means a gene that is identified in the recipient plant or source plants that are sexually compatible with the recipient plant. It does not include genes introduced through genetic engineering from a source organism that is not sexually compatible with the source plant.

* * * * *

Sexually compatible, when referring to plants, means plants must be capable of forming a viable zygote through the union of two gametes through conventional breeding.

* * * * *

■ 3. Revise § 174.21 to read as follows:

§ 174.21 General qualifications for exemptions.

A plant-incorporated protectant is exempt from the requirements of FIFRA, other than the requirements of § 174.71,

if it meets the exemption criteria in paragraphs (a) through (d) of this section. Plant-incorporated protectants that are not exempt from the requirements of FIFRA under this subpart are subject to all the requirements of FIFRA.

(a) The active ingredient of the plant-incorporated protectant meets the exemption criteria listed in at least one of the sections in §§ 174.25 through 174.50.

(b) When the plant-incorporated protectant is intended to be produced and used in a crop used as food, the residues of the active ingredient of the plant-incorporated protectant are either exempted from the requirement of a tolerance under FFDCA (21 U.S.C. 321 *et seq.*) as listed in subpart W of this part, or no tolerance would otherwise be required.

(c) Any inert ingredient that is part of the plant-incorporated protectant is listed as an approved inert ingredient in subpart X of this part.

(d) For plant-incorporated protectants listed in the subparagraphs below, the exemption applies only if the developer is compliant with the general recordkeeping requirements specified in § 174.73 per sections 8 and 9 of FIFRA, 7 U.S.C. 136f and 136g, and only after compliance with the relevant eligibility determination procedures specified in § 174.90:

(1) Plant-incorporated protectant created through genetic engineering from a sexually compatible plant.

(2) Loss-of-function plant-incorporated protectant.

■ 4. Amend § 174.25 by revising the section heading and the introductory text and adding paragraph (c) to read as follows:

§ 174.25 Active ingredient of a plant-incorporated protectant from a sexually compatible plant created through conventional breeding.

The active ingredient is exempt if all of the following conditions are met:

* * * * *

(c) The genetic material is transferred from the source plant to the recipient plant only through conventional breeding.

■ 5. Add § 174.26 to subpart B to read as follows:

§ 174.26 Active ingredient of a plant-incorporated protectant created through genetic engineering from a sexually compatible plant.

The active ingredient is exempt if the conditions in paragraphs (a) and (b) of this section are met.

(a) The active ingredient is characteristic of the population of plants sexually compatible with the recipient plant and is created through genetic engineering from either an insertion of a native gene into the recipient plant as specified in paragraph (a)(1) of this section or a modification of an existing native gene in the recipient plant as specified in paragraph (a)(2) of this section.

(1) *Insertion.* A native gene is inserted into the genome of the recipient plant and produces a pesticidal 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 to those regulatory regions of the native gene identified in the source plant.

(2) *Modification.* The existing native gene is modified to match corresponding polymorphic sequence(s) in a native allele of that gene using a single source plant as a template.

(b) This exemption does not apply until the requirements in § 174.21(d) have been met.

■ 6. Add § 174.27 to subpart B to read as follows:

§ 174.27 Active ingredient of a loss-of-function plant-incorporated protectant.

The active ingredient is exempt if the following conditions are met:

(a) The genetic material of a native gene is modified using genetic engineering to result in a pesticidal effect through the reduction or elimination of the activity of that gene; and

(b) This exemption does not apply until the requirements in § 174.21(d) have been met.

■ 7. Add § 174.73 to subpart D to read as follows:

§ 174.73 General recordkeeping requirements for exemptions.

For 5 years, starting with the effective date of a plant-incorporated protectant exemption, any person who is required to submit documentation for the determination of eligibility for a plant-incorporated protectant listed under § 174.21(d) must do both of the following:

(a) Maintain documentation of either the request for EPA confirmation or the letter of self-determination (or both, if applicable) along with all supporting documentation for the specific exemption listed in subpart E of this part.

(b) Make the documentation outlined in paragraph (a) of this section available to EPA upon request.

■ 8. Add subpart E to read as follows:

Subpart E—Exemption Eligibility Determination Process and Requirements

Sec.

Subpart E—Exemption Eligibility Determination Process and Requirements

§ 174.90 Determining eligibility.

(a) *Options for determining eligibility.* As required in §§ 174.21(d) and 174.541(c), the developer must notify EPA to be eligible for exemption. Available notification options differ by plant-incorporated protectant. The developer must do at least one of the following:

(1) *EPA confirmation.* Unless permitted in paragraph (a)(2) of this section, a developer must submit a request for EPA confirmation of eligibility in accordance with § 174.93. Any developer may submit a request for EPA confirmation of eligibility in accordance with § 174.93.

(2) *Self-determination.* A developer may submit a letter of self-determination in accordance with § 174.91 if the plant-incorporated protectant qualifies for exemption as one of the following:

(i) A loss-of-function plant-incorporated protectant eligible for exemption under § 174.27.

(ii) [Reserved]

(b) *Where to submit a request for EPA confirmation or letter of self-determination.* A request for EPA confirmation of eligibility or a letter of self-determination must be submitted electronically.

(c) *Claims of confidentiality.* Any claims of confidentiality for information submitted in the request for EPA confirmation or a letter of self-determination must be made in accordance with the procedures outlined in § 174.9.

(d) *Overlapping determinations of eligibility.* If a plant-incorporated protectant is eligible for a self-determination option, a developer may elect to submit a letter of self-determination as well as a request for EPA confirmation of eligibility concurrently or at a later time. If the developer so elects, the letter of self-determination will remain in effect while EPA evaluates the request for confirmation of eligibility.

(e) *Revisiting eligibility determination.* If, at any time after EPA issues a confirmation of eligibility or the letter of self-determination is submitted, EPA becomes aware of information indicating that a plant-incorporated protectant no longer meets the criteria for exemption (*e.g.,* adverse effects reports submitted under § 174.71) or that the self-determination was incorrect, EPA will generally notify the submitter in writing of EPA's intention to initiate a review of eligibility for exemption and may request additional information from the submitter in order to evaluate that eligibility for exemption. Upon conclusion of its review, EPA will notify the submitter in writing of its determination as to whether the plant-incorporated protectant meets the exemption criteria and any actions that will be required should the plant-incorporated protectant be found to not meet the exemption criteria. Under those circumstances, the plant-incorporated protectant may be considered to be noncompliant with FIFRA and subject to possible enforcement by EPA. At any time, if EPA finds or has reason to believe that a plant-incorporated protectant's non-compliance with FIFRA requires immediate action, EPA may take such action, including enforcement, without first informing the submitter of an eligibility review.

(f) *Extension of exemption.* An exemption can be extended in one of two ways. First, if the exempted plant-incorporated protectant is moved through conventional breeding to other plants, the exemption is extended to the subsequent plant-incorporated protectant. Second, to extend the exemption of the plant-incorporated protectant to subsequent genetic engineering events in other plants, the following exemption-specific criteria apply:

(1) *Plant-incorporated protectant created through genetic engineering from a sexually compatible plant.* An exemption extends to a plant-incorporated protectant when that plant-incorporated protectant is genetically engineered by the submitter into another variety of that same plant species, the substance produced is identical to the substance produced in the original recipient plant, and no new modifications were made to the regulatory regions.

(2) *Loss of function plant-incorporated protectant.* An exemption extends to a plant-incorporated protectant when that plant-incorporated protectant is genetically engineered by the submitter into another variety of that same plant species and the same native gene is targeted to create the loss-of-function PIP.

(g) *No duplication necessary.* A developer is not required to submit duplicative requests for eligibility determination or self-determination under both §§ 174.541(c) and 174.21(d), if it has already been submitted for purposes of determining eligibility under § 174.21(d).

§ 174.91 Submitting a letter of self-determination.

To self-determine eligibility for the exemption of a plant-incorporated protectant listed under § 174.90(a)(2), a developer must comply with all of the following requirements.

(a) *When to submit a letter of self-determination.* A letter of self-determination for an exemption must be submitted to EPA prior to engaging in any activity that would be subject to FIFRA absent an exemption.

(b) *Contents of a letter of self-determination.* The letter of self-determination must:

(1) Provide the name and contact information for the submitter (including telephone number and email address), company name, or other affiliation.

(2) Identify the plant-incorporated protectant by providing: the identity of the recipient plant (genus and species), a unique identifier for the native gene from the National Center for Biotechnology Information (NCBI) at the National Library of Medicine of the National Institutes of Health (NLM) at the National Institutes of Health (NIH) (*i.e.,* Entrez GeneID), the trait type (*e.g.,* insect resistance), and cite the paragraph under § 174.90(a)(2) that indicates that the plant-incorporated protectant is eligible for self-determination.

(3) Complete and submit the certification statement provided in the electronic submission portal. The statement must be dated and signed by the certifying official identified in the certification statement.

(c) *EPA response.* EPA will provide electronic confirmation of receipt immediately. Electronic confirmation of receipt shall be equivalent to written confirmation of receipt.

(d) *Effective date of exemption.* The exemption does not apply until EPA confirms receipt of the letter of self-determination.

§ 174.93 Requesting EPA confirmation.

To request EPA confirmation of eligibility for exemption of a plant-incorporated protectant listed under § 174.21(d), a developer must comply with all of the following requirements.

(a) *When to submit a request for EPA confirmation.* Unless the developer has received confirmation of receipt of a letter of self-determination, the request for EPA confirmation must be submitted prior to engaging in any activity that would be subject to FIFRA absent an exemption.

(b) *Contents of a request for EPA confirmation of exemption eligibility.* The request must contain information as specified in § 174.91(b) and supporting documentation, as specified in exemption-specific sections of this subpart (*e.g.,* § 174.95).

(c) *EPA review and response.* Upon receipt of a request, EPA will review and evaluate the information provided to determine whether the plant-incorporated protectant meets the exemption criteria in § 174.21. EPA may require additional information to assess whether a plant-incorporated protectant meets the criteria for exemption. EPA will notify the submitter in writing of its determination. If EPA determines that the plant-incorporated protectant does not meet the criteria for exemption, EPA will notify the submitter in writing of any actions that will be required.

(d) *Effective date of exemption.* If the plant-incorporated protectant is not already exempt pursuant to the self-determination process under § 174.91, this exemption applies once EPA notifies the submitter in writing, confirming that the plant-incorporated protectant meets the criteria for exemption.

§ 174.95 Documentation for an exemption for a plant-incorporated protectant created through genetic engineering from a sexually compatible plant.

A developer requesting EPA confirmation of exemption eligibility for a plant-incorporated protectant created through genetic engineering from a sexually compatible plant pursuant to § 174.93 must submit the information in the following paragraphs to EPA. The following documentation must be maintained by a developer of a plant-incorporated protectant created through genetic engineering from a sexually compatible plant per § 174.73:

(a) *Biology of the plant.* (1) The identity of the recipient plant, including genus and species.

(2) If the plant-incorporated protectant was derived from a plant species other than the recipient plant species, provide the identity of the source plant including genus and species and information to support the determination that the recipient plant and the source plant are sexually compatible (*e.g.,* through peer-reviewed literature rationale).

(b) *Description of the pesticidal trait and how the trait was engineered into*

the plant. Include a description of the measures that were taken to ensure that no engineering components (*e.g.,* Cas proteins) are present in the final plant product and the measures taken to maximize the likelihood that the modification to the recipient plant is limited to the intended modification.

(c) *Molecular characterization of the plant-incorporated protectant.* A nucleic acid sequence comparison of the plant-incorporated protectant between the recipient plant and the comparator(s). A deduced amino acid sequence comparison is additionally required when the pesticidal substance is proteinaceous. The relevant comparator(s) for the sequence comparison(s) are determined by the type of modification:

(1) For § 174.26(a)(1), sequences in the source plant and in the recipient plant.

(2) For § 174.26(a)(2), sequences in the recipient plant before the modification, after the modification, and the sequence in the source plant. The polymorphic site(s) must be indicated.

(d) *Information on the history of safe use of the plant-incorporated protectant.* (1) If the pesticidal substance is a known allergen or mammalian toxin/toxicant (*e.g.,* solanine), describe how conventional breeding practices are being used to ensure that it does not exceed human dietary safety levels in the recipient food plant (*i.e.,* ensure residues of pesticidal substance are not present in food at levels that are injurious or deleterious and are within the ranges of levels generally seen in plant varieties currently on the market and/or known to produce food safe for consumption).

(2) If the source plant is a wild relative of the recipient plant, describe why the plant-incorporated protectant is not anticipated to pose a hazard to humans or the environment (*e.g.,* Are levels of the pesticidal substance produced in the recipient plant within the ranges of levels generally seen in plant varieties currently on the market and/or known to produce food safe for consumption? Is the pesticidal mode of action non-toxic? Does the plant-incorporated protectant lack sequence similarity to known mammalian toxins, toxicants, or allergens? Is the plant-incorporated protectant a commonly screened substance and therefore familiar to plant breeders?).

§ 174.96 Documentation for an exemption for a loss-of-function plant-incorporated protectant.

A developer requesting EPA confirmation of exemption eligibility for a loss-of-function plant-incorporated protectant pursuant to § 174.93 must submit the information in the following paragraphs to EPA along with the developer's request for exemption confirmation. The following documentation must be maintained by a developer of a loss-of-function plant-incorporated protectant per § 174.73:

(a) Biology of the plant: The identity of the recipient plant, including genus and species.

(b) Description of the pesticidal trait that results from the loss-of-function and how the trait was engineered into the plant. Include a description of the steps that were taken to ensure that no engineering components (*e.g.,* Cas proteins) remain in the plant and the measures taken to maximize the likelihood that the modification to the recipient plant is limited to the intended modification.

■ 9. Amend § 174.508 by:

■ a. Revising the section heading and introductory text;

■ b. Redesignating paragraph (c) as paragraph (d); and

■ c. Adding a new paragraph (c).

These revisions and addition read as follows:

§ 174.508 Pesticidal substance of a plant-incorporated protectant from a sexually compatible plant created through conventional breeding; exemption from the requirement of a tolerance.

Residues of a pesticidal substance are exempt from the requirement of a tolerance if all the following conditions are met:

* * * * *

(c) The genetic material is transferred from the source plant to the recipient plant only through conventional breeding.

* * * * *

■ 10. Add § 174.541 to read as follows:

§ 174.541 Pesticidal substance of a plant-incorporated protectant created through genetic engineering from a sexually compatible plant; exemption from the requirement of a tolerance.

Residues of a pesticidal substance are exempt from the requirements of a tolerance if the conditions in paragraphs (a) through (c) of this section are met.

(a) The pesticidal substance is characteristic of the population of plants sexually compatible with the recipient food plant and is created through genetic engineering from either an insertion of a native gene into the recipient food plant as specified in paragraph (a)(1) of this section or a modification of an existing native gene in the recipient food plant as specified in paragraph (a)(2) of this section.

(1) *Insertion.* A native gene is inserted into the genome of the recipient food plant and produces a pesticidal 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 to those regulatory regions of the native gene identified in the source plant.

(2) *Modification.* The existing native gene is modified to match corresponding polymorphic sequence(s) in a native allele of that gene using a single source plant as a template.

(b) The residues of the pesticidal substance are not present in food from the plant at levels that are injurious or deleterious to human health.

(c) This exemption does not apply until the requirements in § 174.90 have been met.

[FR Doc. 2023–11477 Filed 5–30–23; 8:45 am]

BILLING CODE 6560–50–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 417, 422, 423, 455, and 460

[CMS–4201–CN]

RIN 0938–AU96

Medicare Program; Contract Year 2024 Policy and Technical Changes to the Medicare Advantage Program, Medicare Prescription Drug Benefit Program, Medicare Cost Plan Program, and Programs of All-Inclusive Care for the Elderly; Correction

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Final rule; correction.

SUMMARY: This document corrects technical errors that appeared in the final rule published in the **Federal Register** on April 12, 2023, entitled ''Contract Year 2024 Policy and Technical Changes to the Medicare Advantage Program, Medicare Prescription Drug Benefit Program, Medicare Cost Plan Program, and Programs of All-Inclusive Care for the Elderly.''

DATES: This correcting document is effective June 5, 2023.

FOR FURTHER INFORMATION CONTACT: Lucia Patrone, (410) 786–8621.

SUPPLEMENTARY INFORMATION:

I. Background

In FR Doc. 2023–07115 of April 12, 2023 (88 FR 22120), there were a