**Shows final revisions made during EO 12866 Review**

**Changes made at OMB's suggestion are identified by yellow highlighting.**

**ENVIRONMENTAL PROTECTION AGENCY**

**40 CFR Part 174**

**[EPA–HQ–OPP–2006–0642; FRL–8100–7]**

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**RIN 2070-AD49**

**Exemption under the Federal Insecticide, Fungicide, and Rodenticide Act for Certain Plant-Incorporated Protectants Derived from Plant Viral Coat Protein Gene(s) (PVCP-PIPs); Supplemental Proposal**

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**AGENCY**: Environmental Protection Agency (EPA).

**ACTION**: Proposed rule.

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**SUMMARY**: EPA is proposing to exempt from Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requirements plant-incorporated protectants derived from plant viral coat protein genes (PVCP-PIPs) when the PVCP-PIP meets specified criteria. EPA is proposing this exemption because the Agency believes that the PVCP-PIPs covered by this exemption would be of a character which is unnecessary to be subject to FIFRA in order to carry out the purposes of the Act.

**DATES:** Comments must be received on or before [*insert date 90 days after date of publication in the* **Federal Register**]

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**ADDRESSES:** Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2006–0642, by one of the following methods:

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- *Federal eRulemaking Portal*: *http://www.regulations.gov/*. Follow the on-line instructions for submitting comments.
- *Mail*: Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.
- *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket telephone number is (703) 305-5805.

*Instructions*: Direct your comments to docket ID number EPA–HQ–OPP–2006–0642. EPA's policy is that all comments received will be included in the docket without change and may be made available on-line at *http://www.regulations.gov*, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through regulations.gov or e-mail. The Federal regulations.gov website is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA without going through regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of special characters, any form of encryption, and be free of any defects or viruses.

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*Docket*: All documents in the docket are listed in the docket index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket telephone number is (703) 305-5805.

**FOR FURTHER INFORMATION CONTACT:** Melissa Kramer, Hazard Assessment Coordination and Policy Division (7202M), Office of Science Coordination and Policy, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: 202-564-8497; fax number: 202-564-8502; e-mail address: *kramer.melissa@epa.gov*.

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**SUPPLEMENTARY INFORMATION:**

## I. General Information

### *A. Does This Notice Apply to Me?*

You may be potentially affected by this action if you are a person or company involved with agricultural biotechnology that may develop and market plant-incorporated protectants. Potentially affected entities may include, but are not limited to:

• Pesticide and Other Agricultural Chemical Manufacturing (NAICS code 32532), e.g., establishments primarily engaged in the formulation and preparation of agricultural and household pest control chemicals

• Crop Production (NAICS code 111), e.g., establishments primarily engaged in growing crops, plants, vines, or trees and their seeds

• Colleges, Universities, and Professional Schools (NAICS code 611310), e.g., establishments of higher learning which are engaged in development and marketing of virus-resistant plants

• Research and Development in the Physical, Engineering, and Life Sciences (NAICS code 54171), e.g., establishment primarily engaged in conducting research in the physical, engineering, or life sciences, such as agriculture and biotechnology

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. To determine whether you or your business may be affected by this action, you should carefully examine the applicability provisions in 40 CFR part 174**.** If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

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*B. What Should I Consider as I Prepare My Comments for EPA?*

1. *Docket.* EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2006–0642. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the Office of Pesticide Programs (OPP) Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Building), 2777 S. Crystal Drive Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket telephone number is (703) 305-5805.

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2. *Tips for preparing your comments.* When submitting comments, remember to:

i. Identify the document by docket ID number and other identifying information (subject heading, **Federal Register** date, and page number).

ii. Follow directions. The Agency may ask you to respond to specific questions or organize comments by referencing a Code of Federal Regulations (CFR) part or section number.

iii. Explain why you agree or disagree; suggest alternatives and substitute language for your requested changes.

iv. Describe any assumptions and provide any technical information and/or data that you used.

v. If you estimate potential costs or burdens, explain how you arrived at your estimate in sufficient detail to allow for it to be reproduced.

vi. Provide specific examples to illustrate your concerns and suggest alternatives.

vii. Explain your views as clearly as possible, avoiding the use of profanity or personal threats.

viii. Make sure to submit your comments by the comment period deadline identified.

## II. Background

*A. What Action is the Agency Proposing?*

EPA is proposing an exemption from FIFRA for certain plant virus coat protein plant-incorporated protectants or "PVCP-PIPs." EPA is proposing to define a PVCP-PIP as "a plant-incorporated protectant derived from one or more genes that encode a coat protein of a virus that naturally infects plants. This includes plant-incorporated protectants derived from one or more plant viral coat protein genes that produce only RNA and no virus-related protein." PVCP-PIPs introduced into plants with the intention of preventing or mitigating viral disease meet the FIFRA section 2(u) definition of "pesticide" because they are introduced into plants with the intention of "preventing, destroying, repelling, or mitigating any pest…" (7 U.S.C. 136(u)) and plant viruses meet the FIFRA section 2 definition of "pest" (7 U.S.C. 136(t)). EPA is proposing this exemption because the Agency believes that the PVCP-PIPs covered by this exemption would be of a character which is unnecessary to be subject to FIFRA in order to carry out the purposes of the Act.

A PIP can be exempt from the requirements of FIFRA, other than the adverse effects reporting requirements of 40 CFR 174.71, if it meets all three of the requirements listed in 40 CFR 174.21. Section 174.21(a) requires that the PIP meet the criteria listed in at least one of the sections in §§ 174.25 through 174.50. Section 174.21(b) requires that when the PIP is intended to be produced and used in a crop used as food, the residues of the PIP are either exempted from the requirement of a tolerance under FFDCA or no tolerance would otherwise be required for the PIP. Section 174.21(c) requires that an exempt PIP must contain only those inert ingredient(s) included on the list codified at §§ 174.485 through 174.490. (Reference to §§ 174.485 through 174.490 in § 174.21(c) is proposed to be changed to refer to §§ 174.485 through 174.486 in today's Proposed Rule.) See Unit II.F. for further discussion of these § 174.21 criteria.

The rule proposed in today's **Federal Register** would establish 40 CFR 174.27, which would contain three criteria that, when met, would allow PVCP-PIPs to meet the general requirement for exemption for all PIPs listed at 40 CFR 174.21(a). Today's **Federal Register** also proposes to add several substances known to be used as inert ingredients in PIPs to 40 CFR part 174 subpart X, thereby potentially expanding the PVCP-PIPs that could meet the conditions of § 174.21(c). A companion document published elsewhere in today's **Federal Register** also proposes a tolerance exemption for certain PVCP-PIP residues, thereby potentially expanding the PVCP-PIPs that could meet the conditions of 174.21(b).

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The three criteria that EPA is proposing to insert at 40 CFR 174.27 are intended to address three issues that may be associated with a PVCP-PIP. These issues are:

• The potential for increased weediness or invasiveness of the crop plant containing the PVCP-PIP or any wild or weedy relatives that could acquire the PVCP-PIP through gene flow thereby causing negative effects on either the agro-ecosystem or natural environments. This issue is addressed in proposed § 174.27(a).

• The potential that viruses with novel properties could develop through novel viral interactions. This issue is addressed in proposed § 174.27(b).

• The potential for human or nontarget organism exposure to proteins that have not previously existed in nature and thus should be examined to determine whether they have potentially toxic or allergenic properties. This issue is addressed in proposed § 174.27(c).

In order to satisfy 40 CFR 174.21(a), a PVCP-PIP would have to satisfy proposed §§ 174.27(a), (b), and (c). The requirements at § 174.27(d) would also have to be met to qualify for exemption. Proposed §§ 174.27(a), (b), and (c) each can be met in one of two ways: a product developer may self-determine that paragraph (1) of the criterion applies (i.e., § 174.27(a)(1), (b)(1), or (c)(1)) or the Agency may determine that paragraph (2) of the criterion applies (i.e., § 174.27(a)(2), (b)(2), or (c)(2), respectively). Paragraph (1) of each proposed criterion (i.e., § 174.27(a)(1), (b)(1), and (c)(1)) describes an objective, well-defined characteristic. Therefore, the developer may determine whether the PVCP-PIP meets the requirement. Paragraph (2) of each proposed criterion (i.e., § 174.27(a)(2), (b)(2), and (c)(2)) is conditioned on an Agency determination because it may involve analysis of several types of information. Each criterion may be satisfied either by self determination under paragraph (1) or Agency determination under paragraph (2) irrespective of how the other two criteria are satisfied; there is no requirement that all three criteria must be satisfied under either paragraph (1) or paragraph (2) in order to qualify for the exemption.

*B. What is the Agency's Authority for Taking this Action?*

This rule is promulgated under the authority of FIFRA sections 3(a), 25(a), and 25(b) (7 U.S.C. 136a(a), 136w(a), and 136w(b)).

FIFRA section 3(a) states that, except as provided by the Act, no person may distribute or sell in the United States any pesticide that is not registered under the Act (7 U.S.C. 136(a)). FIFRA section 2(u) defines "pesticide" as: "(1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and (3) any nitrogen stabilizer…" (7 U.S.C. 136(u)). Under FIFRA section 2(t), the term "pest" includes "(1) any insect, rodent, nematode, fungus, weed, or (2) any other form of terrestrial or aquatic plant or animal life or virus, bacteria, or other microorganism… which the Administrator declares to be a pest…" subject to certain exceptions (7 U.S.C. 136(t)).

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Before EPA may register a pesticide under FIFRA, the applicant must show that the pesticide "when used in accordance with widespread and commonly recognized practice… will not generally cause unreasonable adverse effects on the environment" (7 U.S.C. 136a(c)(5)(D)). The term "environment" includes "water, air, land, and all plants and man and other animals living therein, and the interrelationships which exist among these" (7 U.S.C. 136(j)). FIFRA section 2(bb) defines the term "unreasonable adverse effects on the environment" to mean: "(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 408 of the Federal Food, Drug, and Cosmetic Act" (7 U.S.C. 136(bb)).

Although FIFRA requires the registration of most pesticides, it also authorizes the regulation of unregistered pesticides. FIFRA section 3(a) provides that, to the extent necessary to prevent unreasonable adverse effects on the environment, the Administrator may limit the distribution, sale, or use of any pesticide that is not registered under section 3 of FIFRA, subject to an experimental use permit under section 5 of FIFRA, or subject to an emergency exemption under section 18 of FIFRA. Pesticides that are "not registered" include pesticides that are exempt from FIFRA requirements under section 25(b).

An unregistered pesticide may be distributed or sold if it is exempted by regulation under FIFRA section 25(b). Under FIFRA section 25(b)(2), the Agency can exempt pesticides from some or all of the requirements of FIFRA when the Agency determines that the pesticide is "of a character which is unnecessary to be subject to [FIFRA] in order to carry out the purposes of this Act" (7 U.S.C. 136w(b)(2)). EPA interprets section 25(b)(2) to authorize the Agency to exempt a pesticide or category of pesticides that EPA determines (1) poses a low probability of risk to the environment and (2) is not likely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight under FIFRA. This standard differs from the standard for registration which considers only whether the pesticide "when used in accordance with widespread and commonly recognized practice… will not generally cause unreasonable adverse effects on the environment" (7 U.S.C. 136a(c)(5)(D)).

In evaluating the first condition that must be met for the Agency to exempt a pesticide, i.e., whether use of the pesticide poses a low probability of risk to the environment, EPA considers the extent of the potential risks caused by use of the pesticide to the environment, including humans and other animals, plants, water, air and land. Potential risks to humans include dietary risks as well as non-dietary risks such as those resulting from occupational or residential exposure to the pesticide. EPA uses the FFDCA section 408 standard in evaluating dietary risks as discussed in Unit II.C. of this preamble. EPA will not exempt pesticides unless they pose a low probability of risk to the environment.

In evaluating the second condition that must be met for the Agency to exempt a pesticide, i.e., whether the use of the pesticide is unlikely to cause unreasonable adverse effects on the environment even in the absence of regulatory oversight under FIFRA, EPA balances all the potential risks to human health, including dietary risks (see Unit

II.C. of this preamble for discussion of the FFDCA standard), and risks to the remainder of the environment from use of the pesticide against the potential benefits associated with its use. In balancing risks and benefits, EPA considers the economic, social, and environmental costs and benefits of the use of the pesticide. If the pesticide poses a low probability of risk to the environment and is not likely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight under FIFRA, EPA may exempt the pesticide from regulation under FIFRA.

*C. What is the Relationship of FIFRA Exemptions to the FFDCA Section 408 Standard?*

Under FFDCA section 408(a), a pesticide chemical residue in or on a food (hereafter simply "in food") is not considered safe unless EPA has issued a tolerance for the residue and the residue is within the established tolerance limit or EPA has issued an exemption from the requirement of a tolerance for the residue (21 U.S.C. 346a(a)(1)). FFDCA section 408 authorizes EPA to determine a residue is safe and therefore exempt from the requirement of a tolerance if the Administrator "has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information" (21 U.S.C. 346a(c)(2)(A)(ii)). Section 408 of the FFDCA also directs EPA to specifically consider harm that may result to infants and children as a result of pesticide chemical residues. For additional discussion of this standard, see the Exemption from the Requirement of a Tolerance under the Federal Food, Drug, and Cosmetic Act for Residues of Plant Virus Coat Proteins that are Part of a Plant-Incorporated Protectant published concurrently in today's **Federal Register**.

EPA uses the FFDCA section 408 safety standard in evaluating whether a pesticide used in food meets the FIFRA section 25(b)(2) exemption standard with respect to human dietary risk. A pesticide in food poses a low probability of human dietary risk if it meets the FFDCA section 408 standard for an exemption from the requirement of a tolerance. Such a pesticide also is not likely to cause unreasonable adverse effects to the environment, with respect to human dietary risk only, if the dietary risks resulting from use of that pesticide are consistent with the FFDCA section 408 exemption standard, and the potential benefits of use outweigh any dietary risk even in the absence of regulatory oversight.

FIFRA, however, does not provide for exemption of a pesticide in food based solely upon human dietary risk and consistency with the FFDCA section 408 exemption standard; an exemption from the requirements of FFDCA does not exempt a product from regulation under FIFRA. For an exemption under FIFRA, EPA must also evaluate non-dietary risks to humans and the remainder of the environment from the pesticide and determine both that the pesticide poses only a low probability of non-dietary risks and that use of the pesticide is not likely to cause any unreasonable adverse effects to the environment from such nondietary risks in the absence of regulation.

*D. What is the Role of Other Federal Agencies?*

EPA is the Federal agency responsible for the regulation of pesticides. Under the Coordinated Framework for Regulation of Biotechnology (51 FR 23302, June 26, 1986),

EPA works closely with the U.S. Department of Agriculture (USDA), which has responsibilities under the Plant Protection Act (PPA), and the U.S. Food and Drug Administration (FDA), which has responsibilities under FFDCA. EPA, USDA, and FDA consult and exchange information when such consultation is helpful in resolving safety questions. The three agencies also strive for consistency between programs following one of the basic tenets of the Coordinated Framework, i.e., that the agencies composing the Framework adopt consistent approaches to the extent permitted by the respective statutory authorities. A consistent approach between agencies is easier for the regulated community to understand, and it likely conserves resources because data developed for one agency may meet at least some of the requirements posed by another agency for the same or similar products.

1. *USDA*. USDA has the responsibility of preventing the introduction and dissemination of plant pests under the PPA. Before a genetically engineered plant that is subject to the PPA may be introduced into the environment, approval must be obtained from the USDA/Animal Plant Health Inspection Service (APHIS) unless such a plant has been reviewed and granted Nonregulated Status. The USDA regulations use genetic engineering and potential plant pest risk as criteria for determining the scope of its regulations (62 FR 23945, May 2, 1997). Any genetically engineered plant that contains genetic material from a plant pest is subject to the regulations. Thus, all plants containing PVCP-PIPs are subject to USDA/APHIS requirements under the PPA.

EPA therefore recognizes that there is a potential for duplicative oversight with respect to certain issues that may arise in decisions about PVCP-PIPs that require any review by EPA. For example, in its reviews of Petitions for Determination of Nonregulated Status under regulations at 7 CFR part 340, the potential for weediness, for displacement of native species, and potential consequences of gene transfer are evaluated by USDA/APHIS. EPA and USDA/APHIS will continue to consult and collaborate on reviews of PVCP-PIPs. EPA and USDA/APHIS will work together to avoid potential duplication and inconsistencies and to coordinate their analyses in accordance with their respective expertise and jurisdiction.

2. *FDA*. FDA is the primary U.S. agency responsible for ensuring the safety of commercial food and food additives. FDA's authority under FFDCA extends to any nonpesticidal substance that may be introduced into a new plant variety and that is expected to become a component of food. Pursuant to sections 201 and 408 of FFDCA and the creation of EPA, pesticide chemical residues are subject to EPA's regulatory authority under FFDCA.

*E. What is a PVCP-PIP?*

EPA is proposing to define a PVCP-PIP as "a plant-incorporated protectant derived from one or more genes that encode a coat protein of a virus that naturally infects plants. This includes plant-incorporated protectants derived from one or more plant viral coat protein genes that produce only RNA and no virus-related protein."

Coat proteins are those substances that viruses produce to encapsulate and protect the viral nucleic acid and to perform other important tasks for the virus, e.g., assistance in

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viral replication, movement within the plant, and transmission of the virus from plant to plant by insects (Ref. 1). In many cases, when the genetic material encoding a plant virus coat protein is engineered into a plant's genome, the plant displays resistance to infection by that virus as well as other viruses having similar coat protein sequences (Ref. 2).

Current scientific information suggests that prevention or mitigation of disease by PVCP-PIPs may occur by two different mechanisms. For some PVCP-PIPs, resistance is believed to be protein-mediated because efficacy is correlated with the concentration of coat protein produced by the transgene (Ref. 3). In protein-mediated resistance, the coat protein is thought to impede the infection cycle by interfering with the disassembly of infecting viruses (Ref. 4).

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In transgenic plants, a second mechanism of resistance, post-transcriptional gene silencing (PTGS) may be activated. In PTGS, prevention or mitigation of viral disease is not correlated with the level of coat protein expression. Indeed, virus resistance can occur even when a coat protein gene expresses untranslatable RNA sequences and no coat protein is detected (Ref. 4). PTGS is a defense mechanism in plants against foreign RNA (e.g., viruses) in which sequence-specific RNA degradation is initiated by the plant in response to the foreign RNA itself. Evidence suggests that PTGS is initiated once there is a threshold accumulation of double-stranded (ds) RNA in the cell cytoplasm (Ref. 5). Over 90% of plant viruses have single-stranded RNA genomes, but viral replication transiently produces dsRNA in quantities sufficient to trigger PTGS (Ref. 6). PTGS is also known to occur with transgenes that are transcribed at a low level but that likely produce dsRNA (Ref. 7). Once the plant recognizes the dsRNA, it is thought to be cleaved by a dsRNA-specific nuclease to produce small 21- to 25-nucleotide short interfering RNA sequences (siRNAs; Ref. 8). The siRNAs are thought to serve as guides for the cleavage of single-stranded RNA with a sequence similar to the dsRNAs (Ref. 9). Thus once PTGS is initiated, it targets all RNA with high sequence similarity to the sequence that initiated the process, regardless of whether it was transcribed from the transgene, an endogenous gene, or viral RNA.

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A plant virus coat protein transgene that confers virus resistance through either a protein- or RNA-mediated mechanism would fall within EPA's proposed definition of a PVCP-PIP. The substances involved in either mechanism of resistance would meet the FIFRA definition of a pesticide because the transgene and any material expressed from the transgene are introduced into a plant for the purpose of preventing or mitigating viral disease (see Unit II.A.).

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The proposed definition of a PVCP-PIP contains the phrase "naturally infects plants." Including this phrase in the definition would specifically limit the proposed exemption by requiring that the virus coat protein gene sequence used in the PVCP-PIP be based exclusively on a *plant* virus sequence. This limitation is proposed in order to exclude from the definition any coat proteins of plant viruses that have been modified with sequences from animal or human viruses. EPA includes this concept in today's proposal in response to comment received from the public in earlier **Federal Register** documents pertaining to PVCP-PIPs.

*F. What Conditions Must be Met for a PVCP-PIP to Qualify for a FIFRA Exemption?*

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As noted above, a PIP is exempt from the requirements of FIFRA, other than the adverse effects reporting requirements of 40 CFR 174.71, if the PIP meets the requirements in 40 CFR 174.21(a), (b), and (c). Therefore, the following factors need to be considered to determine the FIFRA status of a PVCP-PIP. First, does the PVCP-PIP meet the requirement at 40 CFR 174.21(a)? Second, do the residues of the PVCP-PIP meet the requirement at 40 CFR 174.21(b)? Third, do the inert ingredients that are part of the PVCP-PIP meet the requirement at 40 CFR 174.21(c)?

1. *Does the PVCP-PIP meet the requirement at 40 CFR 174.21(a)?* Section 174.21(a) requires that the PIP meet the criteria listed in at least one of the sections in §§ 174.25 through 174.50. Today's action proposes to establish § 174.27, which would contain criteria allowing certain PVCP-PIPs to meet the § 174.21(a) requirement for exemption. These criteria identify those PVCP-PIPs that EPA has been able to determine meet the standard under FIFRA section 25(b)(2), i.e., that pose a low probability of risk to the environment and that are not likely to cause unreasonable adverse effects to the environment even in the absence of regulatory oversight under FIFRA. EPA is proposing criteria that address the relevant potential risks associated with these products:

i. The potential for increased weediness or invasiveness of the crop plant containing the PVCP-PIP or any wild or weedy relatives that could acquire the PVCP-PIP through gene flow thereby causing negative effects on either the agro-ecosystem or natural environments. This issue is addressed at § 174.27(a) and is referred to as "weediness" for the purposes of this document.

ii. The potential for viruses with novel properties developing through novel viral interactions. This issue is addressed at § 174.27(b) and is referred to as "viral interactions" for the purposes of this document.

iii. The potential for human or nontarget organism exposure to proteins that may not have previously existed in nature and thus should be examined to determine whether they have potentially toxic or allergenic properties. This issue is addressed at § 174.27(c) and is referred to as "protein production" for the purposes of this document.

Proposed §§ 174.27(a), (b), and (c) are discussed in greater detail in Unit III. of this **Federal Register** document. In addition, a graphical depiction of what this rule is proposing is available in the docket for this proposed rule.

2. *Do the residues of the PVCP-PIP meet the requirement at 40 CFR 174.21(b)?* Section 174.21(b) requires that in order to qualify for a FIFRA exemption, the residues of a PVCP-PIP that is intended to be produced and used in a crop used as food must either be exempted from the requirement of a tolerance under FFDCA or no tolerance would otherwise be required for the PVCP-PIP. Therefore, if a PVCP-PIP is used in a food plant (e.g., the PVCP-PIP is produced and used in a corn plant) or residues of the PVCP-PIP might reasonably be expected in food (e.g., the PVCP-PIP is produced and used in an ornamental plant but could move through gene flow to a sexually compatible food plant), the FFDCA section 408 requirements must be considered when determining whether the PVCP-PIP can be exempted under FIFRA. If a PVCP-PIP would not be used in and would not reasonably be expected in a crop used as food (e.g., the PVCP-PIP is produced

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and used in an ornamental plant with no sexually compatible relatives that are food plants), the FFDCA section 408 requirements do not need to be considered.

EPA anticipates that in most cases the PVCP-PIP residues will consist of residues of nucleic acids, residues of inert ingredients, and residues of the plant virus coat protein portion of the PVCP-PIP (the "PVC-protein"). Residues of nucleic acids are exempt from the requirement of a tolerance at 40 CFR 174.475. As of the time this proposed rule is being issued, residues of those inert ingredients that are exempt from the requirement of a tolerance are listed at 40 CFR 180 and 40 CFR part 174 subpart W. In a companion piece appearing in today's **Federal Register**, EPA is proposing a tolerance exemption for residues of certain PVC-proteins that meet specified criteria. Due to different statutory requirements, the proposed FFDCA exemption criteria differ from the criteria proposed in this **Federal Register** for 40 CFR 174.27 under FIFRA.

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3. *Do the inert ingredients that are part of the PVCP-PIP meet the requirement at 40 CFR 174.21(c)?* Section 174.21(c) requires that in order for a PIP to qualify for exemption any inert ingredient contained in the PIP must be codified at subpart X of 40 CFR Part 174 – List of Approved Inert Ingredients. Subpart X lists the inert ingredients (i) that may be used in a plant-incorporated protectant listed in subpart B (Exemptions) of Part 174 and (ii) whose residues are either exempted from the requirement of a tolerance under FFDCA or no tolerance would otherwise be required. EPA is proposing to add several substances known to be used commonly as inert ingredients in PIPs to 40 CFR 174 subpart X. These substances already have tolerance exemptions under FFDCA. EPA proposes in today's **Federal Register** that these substances, when used in exempt PIPs as inert ingredients under specified conditions, should also be exempt from FIFRA because they are of a character which is unnecessary to be subject to FIFRA in order to carry out the purposes of the Act.

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*G. What if a PVCP-PIP Does Not Qualify for Exemption?*

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If EPA is unable to conclude that a PVCP-PIP meets the standard for exemption, an applicant may still apply to register the PVCP-PIP under section 3 of FIFRA. EPA may be able to conclude that the PVCP-PIP meets the standard for registration (i.e., when it is used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment). EPA recognizes that the proposed exemption criteria may not identify all low risk PVCP-PIPs. A case-by-case review for registration would allow the Agency to evaluate factors not readily incorporated into clear, unambiguous exemption criteria. As part of registration, the Agency could also impose conditions of use as appropriate. As is EPA's general practice regarding registration of PIPs, the Agency will consult with USDA in evaluating PVCP-PIPs for registration.

*H. What is the History of this Proposal?*

1. *Scientific input*. EPA sponsored or cosponsored with other Federal agencies, six conferences relevant to development of this proposed rule: on October 19-21, 1987, a meeting on "Regulatory Considerations: Genetically Engineered Plants" at Cornell University in Ithaca, New York; on September 8-9, 1988, a "Transgenic Plant

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Conference" in Annapolis, Maryland; on November 6-7, 1990, a conference on "Pesticidal Transgenic Plants: Product Development, Risk Assessment, and Data Needs" in Annapolis, Maryland; on April 18-19, 1994, a "Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops" in Annapolis, Maryland; on July 17-18, 1997, a "Plant Pesticide Workshop" in Washington, DC; and on December 10-12, 2001 a conference on "Assessment of the Allergenic Potential of Genetically Modified Foods" in Chapel Hill, North Carolina. EPA incorporated information from these conferences in development of this proposed rule as appropriate.

EPA has requested the advice of two scientific advisory bodies at five meetings while developing its approach to plant-incorporated protectants. On December 18, 1992, EPA convened a FIFRA Scientific Advisory Panel (SAP) to review a draft policy on PIPs (then called plant-pesticides) and to respond to a series of related questions posed by the Agency dealing primarily with EPA's approach under FIFRA. On July 13, 1993, EPA requested the advice of a Subcommittee of the EPA Biotechnology Science Advisory Committee (BSAC) on a series of scientific questions dealing with EPA's approach to PIPs under FFDCA. On January 21, 1994, EPA asked for advice on the Agency's approach to PIPs under both statutes at a joint meeting of the SAP and the BSAC. To evaluate more recent scientific advances, EPA again brought these issues to a FIFRA SAP meeting on October 13-14, 2004. On December 6-8, 2005, EPA convened a SAP meeting to address a series of scientific questions related to this proposal. EPA incorporated advice from all five meetings in development of this proposed rule as appropriate.

2. ***Federal Register** documents*. The history of this proposal consists of the original proposed exemption from FIFRA requirements that appeared in the November 23, 1994 **Federal Register** (59 FR 60519); the original proposed exemption from FFDCA tolerance requirements in the November 23, 1994 **Federal Register** (59 FR 60545); and several supplemental documents appearing in the May 16, 1997 **Federal Register** (59 FR 27149), the July 22, 1996 **Federal Register** (61 FR 37891), the April 23, 1999 **Federal Register** (64 FR 19958), and the July 19, 2001 **Federal Register** (66 FR 37772 and 37855).

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i. *November 23, 1994.* In a document that appeared in the November 23, 1994 **Federal Register** (59 FR 60519) (FRL–4755–3), EPA proposed two alternatives under FIFRA section 25(b)(2) to exempt PVCP-PIPs from FIFRA requirements. Option 1 proposed to categorically exempt plant-pesticides derived from coat proteins from plant viruses (now called PVCP-PIPs). Option 2 proposed a more limited exemption covering only those PVCP-PIPs that would have the least potential to confer selective advantage on free-living wild relatives of the plants that could acquire the PVCP-PIP through gene flow (discussed in detail in Unit III.C.3.).

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Elsewhere in the November 23, 1994, **Federal Register** (59 FR 60545) (FRL–4755–4), EPA proposed to exempt from the FFDCA requirement of a tolerance, residues of plant virus coat proteins produced and used in living plants as a plant-incorporated protectant (then called a plant-pesticide). The proposed exemption from the requirement of a tolerance read, "Residues of coat proteins from plant viruses, or segments of the coat

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proteins, produced in living plants as plant-pesticides are exempt from the requirement of a tolerance" (59 FR 60547).

ii. *May 16, 1997.* In August of 1996, Congress enacted the Food Quality Protection Act (FQPA), which amended FFDCA and FIFRA. On May 16, 1997, EPA published a supplemental document in the **Federal Register** (62 FR 27149) (FRL–5716–6) to provide the public with an opportunity to comment on EPA's analysis of how certain FQPA amendments to FFDCA and FIFRA applied to the 1994 proposed exemption from the requirement of a tolerance for residues of viral coat proteins produced in plants as part of a PIP. (Today's **Federal Register** terms such entities "PVC-proteins.")

In the 1997 supplemental document, EPA explained how most of the substantive factors that the amended FFDCA requires EPA to consider in evaluating pesticide chemical residues had been considered in the Agency's 1994 proposed tolerance exemption. Even though the Agency may not have used the terminology specified in the FQPA, EPA did take into account most of the factors (e.g., toxicity and consumption patterns) in issuing its 1994 proposal to exempt residues of PVC-proteins, or residues of segments of such proteins, from FFDCA tolerance requirements. EPA therefore sought comment on the requirements imposed by FQPA that the Agency had not addressed in its 1994 proposal, specifically:

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a. EPA's conclusion that there are no substances outside of the food supply that may have a cumulative toxic effect with residues of PVC-proteins,

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b. EPA's conclusion that there are no substances outside of the food supply to which humans might be exposed through non-occupational routes of exposure that are related via a common mechanism of toxicity to residues of PVC-proteins,

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c. Any available information on PVC-proteins causing estrogenic effects,

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d. EPA's rationale, described in greater detail, for concluding that PIPs are likely to present a limited exposure of pesticidal substances to humans in which the predominant route of exposure will be dietary, and

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e. EPA's rationale, described in greater detail, for concluding that the Agency's analysis concerning the dietary safety of food containing PVC-proteins applies to infants and children as well as adults.

Because of the 1996 FQPA, EPA's final determination under FIFRA for PVCP-PIPs in food plants could also be affected by comments on the companion document in today's **Federal Register** that proposes a tolerance exemption for certain PVCP-PIP residues.

iii. *July 22, 1996.* On July 22, 1996, EPA issued a supplemental document (61 FR 37891) (FRL–5387–4) requesting comment on one aspect of its November 23, 1994 **Federal Register** document: how the concept of inert ingredient related to plant-incorporated protectants.

iv. *April 23, 1999.* On April 23, 1999, EPA published a supplemental document in the **Federal Register** (64 FR 19958) (FRL–6077–6) soliciting comment on whether to change the name of pesticides produced and used in living plants.

v. *July 19, 2001.* In July of 2001, EPA published a package of notices related to PIPs in the **Federal Register,** including a supplemental document (66 FR 37855) (FRL–6760–4) that provided the public with additional opportunity to comment on the FIFRA and FFDCA exemptions for PIPs that the Agency proposed in 1994 but had not yet finalized by 2001. EPA also requested comment on the information, analyses, and conclusions pertaining to these PIPs (including PVCP-PIPs) contained in the NRC report entitled "Genetically Modified Pest-Protected Plants: Science and Regulation" (Ref. 10). The public was given an opportunity to comment on a proposal to clarify the language of the original 1994 proposals EPA was considering in response to public comment received on the 1994 proposal. In addition, the Agency requested additional public comment on several scientific issues. Also in the July 19, 2001 **Federal Register** (66 FR 37772) (FRL-6057-7), EPA changed the name of these pesticides from "plant-pesticides" to "plant-incorporated protectants" or "PIPs."

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The documents and reports of the meetings described above, including associated public comments, are available in the public dockets established for the associated rulemakings as described in Unit IX. of this preamble.

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Today's proposed rule completely supersedes these previous proposals. EPA does not intend to respond to comments submitted on those proposals. Thus, individuals who believe that any comments submitted on any of the earlier proposals remain germane to today's proposal, should submit them (or relevant portions) again during this comment period.

## III. Proposed Exemption Criteria under § 174.27

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### *A. Structure of the Proposed Exemption Criteria under § 174.27.*

In order to satisfy the general requirement for a FIFRA exemption listed at 40 CFR 174.21(a), EPA is proposing to add three criteria at 40 CFR 174.27. As discussed in Unit II.F.1., the three criteria that EPA is proposing to adopt at 40 CFR 174.27 are intended to address three issues that are associated with potential risks of PVCP-PIPs.

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The PVCP-PIP would have to meet proposed §§ 174.27(a), (b), and (c) to satisfy 40 CFR 174.21(a). Proposed §§ 174.27(a), (b), and (c) each can be met in one of two ways: a product developer may self-determine that paragraph (1) of the criterion is met (i.e., § 174.27(a)(1), (b)(1), or (c)(1)) or the Agency may determine that paragraph (2) of the criterion is met (i.e., § 174.27(a)(2), (b)(2), or (c)(2), respectively). Paragraph (1) of each proposed criterion (i.e., § 174.27(a)(1), (b)(1), and (c)(1)) describes an objective, well-defined characteristic. Therefore, the developer may determine whether the PVCP-PIP meets the requirement. Paragraph (2) of each proposed criterion (i.e., § 174.27(a)(2), (b)(2), and (c)(2)) is conditioned on an Agency determination because several types of information may need to be evaluated using a weight-of-evidence approach to determine

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whether the PVCP-PIP meets the requirement and is therefore of a nature warranting exemption.

1. *Exemption by self-determination*. Each criterion may be satisfied under either paragraph (1) or paragraph (2) irrespective of how the other two criteria are satisfied; there is no requirement that all three criteria must be satisfied under either paragraph (1) or paragraph (2) in order for a PVCP-PIP to qualify for the exemption. However, if a PVCP-PIP satisfies all three criteria under paragraph (1) by developer self determination (i.e., it meets proposed §§ 174.27(a)(1), (b)(1), and (c)(1)) and it satisfies §§ 174.21(b) and (c), EPA is proposing that the developer submit a notification to the Agency of that determination and certify that the PVCP-PIP qualifies for exemption under FIFRA, i.e., that the PVCP-PIP meets §§ 174.21(a), (b), and (c). In addition, EPA is proposing that the developer maintain information adequate to support the determination. Such records must be made available for EPA inspection and copying or be otherwise submitted to the Agency for review upon request for the duration of time that the PVCP-PIP is sold or distributed. EPA is proposing that these records be kept so that EPA could review a particular exemption determination if needed at a future date.

EPA is proposing to require that the notifications contain:

i. The name of the crop (including genus and species) containing the PVCP-PIP.

ii. The name of the virus from which the coat protein gene was derived.

iii. The name of the virus(es) to which resistance is conferred.

iv. When available, a unique identifier.

EPA is proposing this notification requirement because it provides a mechanism that allows the Agency to keep a record of all PVCP-PIPs that may be sold or distributed. EPA expects that such a list would be useful to developers whose products are moving in international trade because it would enable EPA to post information on the United States Regulatory Agencies Unified Biotechnology Website (found at *http://usbiotechreg.nbii.gov/database_pub.asp*) indicating that the developer has determined that the product satisfies the Agency's safety requirements. Such information can facilitate acceptance by importing countries. Absent such a posting, the field for EPA information would be blank, and importers might question the regulatory status of the product in the United States. In addition, EPA considers that such a list may be useful to the Agency for ensuring enforcement and compliance with FIFRA regulations because it will enable compliance personnel to ascertain the exemption status of products encountered in distribution and trade channels.

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2. *Exemption by Agency determination.* If a PVCP-PIP does not satisfy a particular criterion under paragraph (1) (i.e., § 174.27(a)(1), (b)(1), or (c)(1)), EPA proposes that as an alternative route to exemption, the product developer would submit data or other information to the Agency to demonstrate that a particular PVCP-PIP meets paragraph (2) of that criterion (i.e., it meets § 174.27(a)(2), (b)(2), or (c)(2), respectively). In addition, as part of this submission, a developer would also include a certification as to any determination that the product meets § 174.27(a)(1), (b)(1), and/or (c)(1), as appropriate. During its review under § 174.27(a)(2), (b)(2), and/or (c)(2), EPA would not review the developer's determination that the product met any criterion under § 174.27(a)(1), (b)(1), or (c)(1).

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EPA expects that in many instances developers would have most, if not all the information that would need to be included in any exemption submission under §§ 174.27(a)(2), (b)(2), or (c)(2) because it would have been gathered in the course of product development or for submission to USDA/APHIS as part of a petition for determination for non-regulated status. EPA will consult with USDA in evaluating whether a PVCP-PIP meets the conditions for an Agency-determined exemption. EPA is proposing that information supporting the submission be maintained as records that will be available for EPA inspection as necessary for the duration of time that the PVCP-PIP is sold or distributed.

EPA will evaluate the information contained in the submission and publish a notice allowing the public to comment on the Agency's determination that a product meets §174.27(a)(2), (b)(2), and/or (c)(2), as appropriate. EPA is providing such a public comment period because even though the public will have had the opportunity to comment through this proposal on the appropriateness of the criteria in § 174.27(a)(2), (b)(2), and (c)(2), the public would not otherwise have an opportunity to comment on whether a particular PVCP-PIP meets these criteria, given that these determinations depend on a case-by-case analysis of several types of information.

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The Agency plans to publish a **Federal Register** notice announcing its determination that a PVCP-PIP meets §174.27(a)(2), (b)(2), and/or (c)(2), and if no adverse comments are received during the comment period, the Agency's decision will be considered final, and EPA will publish no further notice. Based on its experience with EUP notices, EPA expects that, in general, determinations that a PVCP-PIP qualifies for exemption will be noncontroversial and generate no adverse comments. However, in the case of adverse comments, EPA would publish a subsequent **Federal Register** notice announcing its final determination and address all public comments. EPA would prefer criteria in §174.27(a)(2), (b)(2), and (c)(2) that would allow the public and PVCP-PIP developers to readily predict the outcome of an Agency review. Such criteria would reduce regulatory uncertainty in PVCP-PIP development and decrease the time EPA would need to evaluate the data/information necessary to make a determination that a PVCP-PIP meets a given criterion. However, using criteria for which determinations can be readily predicted might reduce the number of PVCP-PIPs that would qualify for exemption. EPA tried to balance these concerns and proposed multiple options when the Agency was unsure how to resolve this dilemma.

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However, EPA does not believe that the considerations underlying its decisions to grant the public a further opportunity to comment on the Agency's decision apply in cases where the Agency rejects a submission for an exemption. Accordingly, if EPA determines that the product fails to meet one or more of the exemption criteria, EPA will provide notice to the applicant of its decision on the submission and that a registration would be required for the PVCP-PIP before the PVCP-PIP could be sold or distributed. The product developer may then submit an application for registration to the Agency. EPA would evaluate such PVCP-PIPs under the existing registration process and could implement conditions of use as appropriate.

*B. Key Scientific Issues Associated with the Proposed Exemption Criteria under §174.27.*

Several scientific questions concerning risk issues associated with PVCP-PIPs have been identified:

• What is the potential for a PVCP-PIP to endow plants with characteristics that could disrupt the existing network of ecological relationships in managed, semi-managed, or natural ecosystems, e.g., through gene transfer to wild or weedy[2] relatives? This issue is addressed at proposed § 174.27(a) and is referred to as "weediness" for the purposes of this discussion.

• What is the potential for interactions between a PVCP-PIP and an infecting virus to affect plant virus epidemiology or pathogenicity? This issue is addressed at proposed § 174.27(b) and is referred to as "viral interactions" for the purposes of this discussion.

• What is the potential for exposure of humans or nontarget organisms to PVC-proteins with novel toxic or allergenic properties? This issue is addressed at proposed § 174.27(c) and is referred to as "protein production" for the purposes of this discussion.

These three questions are addressed below under the headings of weediness, viral interactions, and protein production, respectively.

*C. Weediness.*

*1. Scientific issues.* In evaluating whether a PVCP-PIP could alter ecological relationships among plants, EPA considered two primary issues: (1) whether the PVCP-PIP could endow a transgenic plant itself with an increased ability to spread into natural or semi-managed habitats and (2) whether the transfer of a PVCP-PIP from a transgenic plant into wild or weedy relatives could endow the wild or weedy relative with increased competitive ability and thus disrupt ecological relationships. Gene transfer among sexually compatible plants is a natural phenomenon that EPA does not consider to be an

[2] In the context of the phrase "wild and weedy" relatives/plants used throughout this preamble, EPA considers weedy plants to be those with the characteristics of weeds, i.e., those that are considered undesirable, unattractive, or troublesome, especially when growing where they are not wanted. Wild plants are those that occur, grow, and live in a natural state and are not domesticated, cultivated, or tamed. EPA considers a naturalized population to be an enduring population of domesticated plants that grows in wild (non-cultivated) areas. EPA considers a native plant population to be one that originates in a particular region or ecosystem.

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environmental risk per se. Whether the transfer of a PVCP-PIP could significantly disrupt ecological relationships in specific instances depends on all of the following considerations: First, does the crop plant containing the PVCP-PIP have wild relatives with which it is able to hybridize in nature? If it does not, there can be no gene transfer. Second, if there are sexually compatible relatives, is the gene conferring virus resistance likely to become stable in the population? Third, is the stable introduction of a PVCP-PIP into the plant population (i.e., introgression) likely to cause the population to become more weedy/invasive or otherwise alter its competitive ability, thereby significantly changing the population dynamics of the plant community? The 2005 SAP concurred that these are important considerations for PVCP-PIPs by noting that an "important ecological risk associated with gene flow from crop plants into their wild relatives is that the acquisition of crop genes might substantially alter the population dynamics of the wild plant. In particular, a transgene introgressed from the crop relative into a wild population might allow the wild species to persist in larger populations across a larger geographic range, or in a wider range of habitats. Collectively these changes in population dynamics can be considered 'increased weediness'. The probability that a particular transgene will lead to increased weediness depends on the phenotype conferred by the transgene and on the ecological factor(s) currently limiting the size or distribution of the wild species. In particular, if the transgene alters plant response to the ecological factor limiting population size, then population dynamics may be affected. For PVCP-PIPs, the relevant consideration is whether virus resistance (conferred by the PVCP-PIP) leads to changes in the size or distribution of wild plant species with the PVCP-PIP" (Ref. 11).

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i. *Likelihood that a crop plant containing a PVCP-PIP could itself disrupt ecological relationships.* In considering whether a PVCP-PIP could affect the ability of a plant to spread into natural or semi-managed habitat at the margins of cultivated fields, i.e., to form feral or naturalized populations, the key consideration is whether viral infection is currently limiting the ability of agricultural crops to do so. The 2005 SAP pointed out that PVCP-PIPs "are developed when virus infection of a crop reduces the crop yield, suggesting that virus infection is quite likely in naturalized populations of the crop as well" (Ref. 11). However, virus infection in crop plants does not necessarily limit the spread of the crop into natural or semi-managed areas. As the 2005 Panel also noted, "little is known about factors controlling population size in plant populations in general, including those that are currently stable, as well as those that are currently weedy or invasive" (Ref. 11). Few published studies are available that evaluate this question directly, perhaps due to the general rarity of negative results in scientific literature. However, one study did find virus infection to have little effect on an agricultural crop. Field experiments with transgenic virus-resistant sugar beets revealed no competitive advantage (measured as seedling emergence and biomass production) between the transgenic and susceptible control lines (Ref. 12).

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Although virus infection has been shown to negatively impact growth and/or reproduction of some natural plant communities (discussed below in Unit III.C.1.ii.), EPA recognizes that there is reason to question whether the situation would be different for crop plants. The National Research Council (NRC) noted in 1989 that most naturalized, domesticated crops generally are unable to effectively compete with wild species in natural ecosystems and have not been known to acquire this ability with the

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type of single-gene traits commonly introduced through genetic modification (Ref. 13). The 1989 NRC report went on to note that plant breeders have capitalized for decades on the fact that relatively minor genetic changes can produce plants with altered ecological properties, but the addition of pest resistant traits has not been known to result in increased weediness of widely used crops (Ref. 13). A 1989 survey of the weedy characteristics of crop versus weed species showed that weeds possess significantly more weedy characteristics on average than do crop plants (Ref. 14). For domesticated crops, the traits that make them useful to humans also reduce their competitive ability in nonagricultural habitats. Crops that have been subjected to long-term breeding (e.g., corn and soybeans) are unlikely to possess characteristics that would allow the plant to compete effectively outside of managed ecosystems. Domesticity arises because intensive breeding efforts seek to eliminate many characteristics of the crop plant that would enhance weediness (e.g., seed shattering, thorns, seed dormancy, and bitterness). For example, lack of seed shattering and seed dormancy greatly reduces the ability of an annual crop to persist without human intervention. Highly domesticated crops such as corn are thus unlikely to survive for multiple generations outside agricultural fields no matter what transgenic trait they contain, including virus resistance (Ref. 15).

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However, some crop species, e.g., cranberry and blackberry, may have more similarities to their wild relatives than highly domesticated crops such as corn or soybean. As noted by the 2005 SAP, "Determining whether a particular crop can naturalize and then spread as a weedy species is difficult to ascertain from the literature and determining the probability that a crop will be more weedy or invasive if it contains a PVCP-PIP is even more difficult" (Ref. 11). Such determinations may therefore need to rely on information not available in public literature as part of a risk assessment for a particular plant. Plants, such as forest trees, that may grow for many years in natural environments or in very close proximity to natural environments present additional difficulty in evaluating and managing risks (Ref. 16). The period of time over which such plants would persist is significantly longer than for annual, short-lived species. Individual plants will therefore experience a much wider range and variety of stress conditions, enemy attacks, and climate change, making predictions about naturalization potential with acquired virus resistance particularly challenging.

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Thus, although EPA believes that many crop species are unlikely to disrupt ecological relationships through acquisition of a PVCP-PIP, the available information is insufficient to support the general conclusions that EPA would need to make for a categorical exemption of PVCP-PIPs. EPA would need to conclude that there is a low risk that acquisition of a PVCP-PIP would significantly affect the competitiveness of any of the plants currently grown as crops and that none of these crop species would significantly disrupt ecological relationships when modified to contain a PVCP-PIP. Therefore, the Agency believes that it is necessary to evaluate each plant species independently to consider whether it is likely to establish weedy or invasive populations outside of agricultural fields in the United States and thereby potentially significantly disrupt ecological relationships if it becomes virus resistant due to a PVCP-PIP. Factors likely to influence this determination cannot be readily distilled into a straightforward criterion suitable for a categorical exemption.

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ii. *Likelihood that a crop plant containing a PVCP-PIP could significantly disrupt ecological relationships through gene transfer*. The question of whether gene transfer from a crop to a wild or weedy relative could significantly disrupt ecological relationships is a more complicated question because a much broader range of potential plants may be involved when wild or weedy relatives are considered in addition to the crops themselves. The answer to this question depends first on the question of whether the transgenic crop plants could transfer a PVCP-PIP to other plant populations. This potential for transfer depends in part on the frequency of hybridization between domesticated species and their wild relatives. Hybridization is affected by the ability of plants to cross-pollinate which in turn is affected by their timing of reproductive viability and the proximity of the plants. Hybridization is also affected by the ability of pollen to fertilize recipient plants, the recipient plants to develop viable seeds, these seeds to germinate, and the seedlings to grow into viable adults (Ref. 17). In spite of these potential constraints, a survey of the world's most important crops suggests that spontaneous hybridization of domesticated plants with wild relatives appears to be a general feature across at least a portion of the worldwide geographic area over which each is cultivated (Refs. 18 and 19). The ability to cross crops with wild relatives (which may not necessarily occur where the crop is grown) is also the basis of many traditional breeding techniques that are used for virtually all crops (Ref. 20).

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Whether virus infection limits the growth and/or reproductive ability of wild or weedy plant populations is more difficult to answer generically for all plants in all ecosystems. Viruses are pervasive in many natural plant populations (Refs. 21, 22, 23 and 24), although a comprehensive body of literature on the effect of viruses in weed species is lacking. According to the 2004 SAP, "Our knowledge about the effect of virus infection on non-crop plants is quite limited" (Ref. 25). Some published studies report that virus infection can have little or no effect on the plants. For example, a survey of *Plantago* species in England showed that although 92 of 144 plants were infected with one or more viruses, most of the plants showed no obvious disease symptoms (Ref. 23). A literature review of the role of weeds in the occurrence and spread of plant virus diseases describes several cases where viruses significantly damage certain crops but have little effect on their weed hosts (Ref. 26).

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Other published studies have reported that infection reduces plant growth and/or fecundity. For example, naturally occurring tobacco leaf curl virus infection increases mortality and has negative effects on growth and seed output in plants from wild populations of the flowering perennial plant *Eupatorium chinense* (Ref. 27). Greenhouse experiments with this same plant under two irradiance levels showed that virus infection did not affect survivorship under high-light conditions but caused severe damage under low-light conditions (Ref. 28). Vegetative growth and flower production of purslane (*Portulaca oleracea*) was also reduced when plants were inoculated with cucumber mosaic virus (Ref. 29). Field experiments showed that wild cabbage plants (*Brassica oleracea*) inoculated with turnip mosaic virus or turnip yellow mosaic virus have reduced survival, growth, and reproduction (Ref. 30). Such experiments suggest that viruses can sometimes reduce individual plant growth and/or fecundity when infection occurs. However, individual-level effects are insufficient to understand population-level processes. For example, even if virus disease significantly affected individual plant

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fitness, a decline in individual-plant fitness might reduce competition such that uninfected plants could increase reproductive output, thereby mitigating any population-level effects (Ref. 31).

It can be difficult to predict the actual impact on overall plant population dynamics that would result from acquisition of virus resistance by plants that are in some way negatively affected by virus infection. EPA is not aware of any published study that has directly examined this question by, for example, purposefully freeing a plant species from virus infection and investigating the resulting population dynamics of infected versus uninfected plants. The 2004 SAP was also unaware of any such study, but offered that "[b]ased on knowledge obtained from observation of cultivated crops in the agroecosystem, the majority of the Panel concluded that it would be unlikely that a plant population freed from viral pressure would give a plant species a competitive advantage" (Ref. 25). Some members of the 2005 SAP agreed with the 2004 SAP, while "[o]ther members of the current [2005] SAP believed, based on new information (Fuchs et al. 2004; Sukopp et al., 2005) not available to the 2004 Panel, as well as EPA indicating a lack of data on this topic, that concluding that viruses typically have no effect on their wild plant hosts is not accurate. Because of the differing opinions among the current [2005] Panelists, and the general paucity of data, the Panel cautioned that further research is needed to provide stronger support to this particular issue" (Refs. 11, 32 and 33). EPA also notes that evaluating impacts on plant population dynamics is further complicated because in certain cases gene transfer of a PVCP-PIP to wild or weedy relatives might potentially be desirable. For example, an invasive virus species might be effectively controlled through broad acquisition of resistance by plant species susceptible to the virus. Controlling disease outbreaks in perennial agricultural plants and trees could be significantly aided by reducing viral load in the environment through such approaches.

A few studies are available that are relevant to the question of whether acquisition of virus resistance could affect plant population dynamics. These studies show that in some cases virus infection can have such effects, suggesting that acquired virus resistance might as well. For example, infection with alfalfa mosaic virus substantially diminished the ability of certain medic cultivars to compete with other species such as capeweed in grazed pasture swards, both directly by decreasing the competitive ability of infected plants, and indirectly by altering the proportions in which the species germinated (Ref. 34). In another example of virus infection affecting plant population dynamics, growth analysis of *Eupatorium makinoi* revealed that plants naturally infected with a geminivirus had significantly reduced stem growth and plant height, along with decreased flowering and survivorship. This study suggests that in spite of the long-term coexistence of the virus and *Eupatorium makinoi*, such negative fitness attributes have a significant impact on at least some local plant populations in this species (Ref. 35).

Although relatively little research has been published regarding how plant population dynamics are directly influenced by virus infection, such results as described in the previous paragraph provide some support for the premise that virus resistance might be an important ecological fitness characteristic. At least some plant populations acquiring virus resistance might in some instances be able to better compete against other species (Ref. 36) and/or spread to habitats previously unsuitable because of the presence

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of the virus (Ref. 37). For example, a broad survey of geographic data on plant associations with viruses from published compendia and governmental or academic databases showed that plants were infected by 24% fewer viruses in their naturalized ranges than in their native ranges, supporting the hypothesis that the impact of invasive plants results in part from reduced natural enemy (e.g., virus) attack (Ref. 38). On the other hand, enemy release is only one of many hypotheses that could explain the abundance and/or impact of an invasive plant (Ref. 39). In addition, a few published studies have reported that in certain instances virus infection can increase plant fitness, suggesting that acquisition of virus resistance might decrease plant fitness. For example, infection by barley yellow dwarf virus was found in at least one year to increase the fitness of the host plant green foxtail (*Setaria viridis*) by approximately 25% (Ref. 40). In some cases plants might be more attractive to herbivores when not infected by viruses, as was found to be the case for dusky coral pea (*Kennedya rubicunda*; Ref. 41). In this experiment, caged rabbits presented with a mixture of carrots and powdered plant extract grazed the mixture made from virus-free plant material at twice the rate as plant material infected with Kennedya yellow dwarf virus due presumably to greater palatability. In general, negative fitness attributes would be expected to be selected against in populations. Nevertheless, such considerations might be important in certain instances, e.g., when evaluating possible effects on endangered species.

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EPA believes it likely that many of the potential PVCP-PIP/plant combinations pose a low risk of disrupting the existing network of ecological relationships in semi-managed or natural ecosystems. Multiple conditions must be met to pose a higher level of risk, i.e., hybridization with a wild relative must occur, introgression of the gene must occur, and acquired virus resistance must confer an advantage (or disadvantage) to the recipient plant sufficient to alter plant population dynamics. Nevertheless, the research discussed above showing that in some cases viruses can affect plant population dynamics for at least some plants highlights the difficulty in drawing a general conclusion as to whether all PVCP-PIP/plant combinations are likely to pose a low risk of significantly disrupting existing ecological networks. Virtually any crop could be modified to contain a PVCP-PIP, including less domesticated forage crops and trees, and such a wide range of plants will be associated with a concomitantly wide range of characteristics and behaviors. Ecosystems are highly complex and variable, and some of the factors that limit fitness of a given plant species can be subtle and are not well understood (Ref. 15). Consequently, EPA does not believe that the available body of evidence would currently support a definitive conclusion for all PVCP-PIPs that the potential transfer to wild or weedy relatives presents a low risk of significantly altering the network of ecological relationships in semi-managed or natural ecosystems.

Information may be available to evaluate the likelihood of acquired virus resistance impacting a particular plant species or population. However, the existing body of literature currently does not appear sufficient to describe any set of circumstances that would predict for the wide variety of possible PVCP-PIP/plant combinations whether introgression of the PVCP-PIP into a wild or weedy relative could change the population dynamics of the recipient plant and through this route potentially affect ecological relationships with other plants and other organisms in the community. For example, it is not possible to predict *a priori* whether a possible fitness advantage that individual plants

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might acquire with a PVCP-PIP would make the plant population better able to compete against other species. Whether population dynamics would be affected and ecological relationships could be disrupted in a given circumstance is dependent on multiple, interacting factors. In some instances, a weight-of-evidence, case-by-case review of information such as experimental data might allow such a determination; however, general knowledge of factors likely to influence population dynamics cannot be readily distilled into a straightforward criterion suitable for a categorical exemption.

2. *Proposed exemption criterion.* EPA is proposing § 174.27(a) based on a set of considerations articulated by the 2005 SAP to identify plants that would not pose concerns associated with increased weediness of either the crop plant itself or any sexually-compatible wild relatives, if the crop plant were to contain a PVCP-PIP. Section 174.27(a)(1) is a categorical exemption criterion for a subset of PVCP-PIPs, i.e., a list of plants that have already been determined by the Agency to be low risk with respect to concerns associated with weediness irrespective of the particular PVCP-PIP the plants might contain. Section 174.27(a)(2) is a conditional exemption criterion based on Agency review of whether a particular plant/PVCP-PIP combination poses low risk with respect to concerns associated with weediness. Both parts of § 174.27(a) are discussed in more detail in Units III.E.1.iii. and III.E.1.iv. below. Note that a PVCP-PIP qualifies for exemption based in part on its presence in a particular crop species. The record on which this proposed exemption is based is not currently broad enough to support an exemption for a PVCP-PIP in another species if that species has not been evaluated for concerns associated with weediness when it contains a particular virus-resistant trait. A PVCP-PIP that has been moved into another species does not qualify for the exemption unless the recipient plant appears on the list in § 174.27(a)(1). Such a PVCP-PIP would either need an individual exemption determination under § 174.27(a)(2) or a registration in order to be sold or distributed.

i. *Proposed categorical exemption criterion in §174.27(a)(1).* As articulated above, EPA does not believe it can propose a *categorical* exemption based on whether a PVCP-PIP/plant combination is likely to result in changes in plant population dynamics because this endpoint cannot easily be predicted based on straightforward characteristics of the PVCP-PIP and/or plant. However, EPA believes that a criterion for a categorical exemption could be developed based on evaluation of individual crop species for their potential to naturalize and invade natural ecosystems, including with acquisition of a PVCP-PIP and for the existence of wild or weedy relatives that could acquire a PVCP-PIP through gene flow. Certain plants are expected to pose low risk with respect to concerns associated with weediness regardless of any particular PVCP-PIP that the species contained. However, for the categorical exemption, the Agency is attempting to identify those situations where no case-by-case review is necessary to conclude that a PVCP-PIP would present a low risk of causing adverse effects. In such situations, a product developer could use a clearly defined criterion to make a determination of status. Based on these considerations, EPA has developed a list of plants that the Agency proposes a developer could use to self-determine whether § 174.27(a) is met.

A PVCP-PIP would meet proposed § 174.27(a) under § 174.27(a)(1) if the plant containing the PIP is one of the following: Anthurium (*Anthurium* spp.), asparagus

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(*Asparagus officinale*), avocado (*Persea americana*), banana (*Musa acuminata*), barley (*Hordeum vulgare*), bean (*Phaseolus vulgaris*), cacao (*Theobroma cacao*), carnation (*Dianthus caryophyllus*), chickpea (*Cicer arietinum*), citrus (*Citrus* spp., e.g., *Citrus aurantifolia, Citrus limon, Citrus paradisii, Citrus sinensis*), coffee (*Coffea arabica* and *Coffea canephora*), corn (*Zea maize*), cowpea (*Vigna unguiculata*), cucumber (*Cucumis sativus*), gerbera (*Gerbera* spp.), gladiolus (*Gladiolus* spp.), lentil (*Lens culinaris*), mango (*Mangifera indica*), orchids (Orchidaceae), papaya (*Carica papaya*), pea (*Pisum sativum*), peanut (*Arachis hypogaea*), pineapple (*Ananas comosus*), potato (*Solanum tuberosum*), soybean (*Glycine max*), starfruit (*Averrhoa carambola*), sugarcane (*Saccharum officinarum*), or tulips (*Tulipa* spp.).

EPA developed this list of plants after consultations with both the 2004 and 2005 SAPs. The 2004 SAP recommended a longer list of plants, chosen initially based on the presumption that they had no wild or weedy relatives in the United States. However, the 2005 SAP noted that the longer list of plants recommended by the 2004 SAP clearly contained "some species that form viable crop-wild hybrids…" (Ref. 11). Recognizing that much of the most useful information is not likely to be found in the literature, "the Panel recommended consulting agronomists, breeders, and/or ecologists with specialized expertise before including any crop on a list of exempt species" (Ref. 11). The 2005 Panel also recommended a specific set of conditions that each species would have to meet based on the advice of such experts (i.e., agronomists, breeders, and/or ecologists with specialized expertise) if it were to be placed on the list:

1. A crop should be included on the exempt list if it forms no viable hybrids with wild or weedy relatives anywhere in the US…

2. A crop should…be included on the exempt list only if it is [not] currently weedy or invasive…

3. A crop should be included on the exempt list if… it will not establish weedy or invasive populations if it becomes virus resistant (due to a PVCP-PIP)…

4. If a PVCP-PIP crop has the potential to naturalize, but the PVCP-PIP transgene is in biocontainment and/or biomitigation constructs that are stacked such that escapes from cultivation are too unfit to compete with the wild type, a consensus of breeders, agronomists, and ecologists, or others with experience with the species could advise addition to the list (Ref. 11).

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EPA believes that the first three conditions proposed by the 2005 SAP are useful factors in evaluating whether a plant warrants inclusion on the list in § 174.27(a)(1). EPA considered each of these factors when evaluating each of the plants currently on the list in proposed § 174.27(a)(1). However, EPA also recognizes that plants that do not strictly meet condition 1 as laid out by the SAP may nevertheless be determined to pose low risk with respect to weediness concerns after a case-by-case review of the plants' traits and consideration of the whole range of factors that affect weediness. For example, corn may not meet the first condition above as articulated by the SAP if it proves to in fact have wild relatives in some region of the United States with which it can form viable hybrids. However, as discussed below, EPA does not believe that the characteristics of the wild relatives or the hybrids that could be formed suggest any reason to suspect acquired virus resistance would change the weediness potential of corn, the hybrid, or the wild relative, and EPA therefore proposes to include corn on the list. Thus, in practice EPA considers the 2005 SAP's first three conditions as a useful guide of the factors that should be taken

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into account in evaluating whether to include a plant on the list. However, EPA believes that relying on a strict interpretation of these conditions would exclude many plants containing PVCP-PIPs that meet FIFRA's low risk standard. The 2005 SAP itself suggested that some flexibility of interpretation might be appropriate. Although the Panel used the phrase "no viable hybrids" in condition 1, the Panel elsewhere recommended against granting exemption to crops with "sexually compatible wild relatives" where "sexually compatible refers to the possibility of having crop transgenes backcross and introgress into the relative; it does not refer to sterile hybrids" (Ref. 11).

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Although EPA considered the first three conditions proposed by the 2005 SAP in deciding whether to include a particular plant species on the list in § 174.27(a)(1), EPA believes that the fourth condition as articulated would be inappropriate for these purposes. A biocontainment and/or biomitigation construct would be associated with a particular PVCP-PIP, not a particular plant species. The intent of § 174.27(a)(1) is to list species that would not present concerns related to weediness regardless of the particular PVCP-PIP that the species contained. EPA believes that construct-specific considerations could be taken into account under an Agency review procedure such as that described below in Unit III.C.2.iii.

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The Panel recommended "consulting agronomists, breeders, and/or ecologists with specialized (taxon-specific) expertise on weedy populations before including any crop on a list of exempt species" because this information "is difficult to ascertain from the literature and determining the probability that a crop will be more weedy or invasive if it contains a PVCP-PIP is even more difficult." Likewise, the Panel indicated "[i]t is very difficult to identify crops that have no sexually compatible wild or weedy relatives in the US or its possessions and that do not become weedy or invasive themselves. This information is unique to each crop, is often not published, and is often known only by the agronomists, breeders, and ecologists working with the specific taxa in question" (Ref. 11). EPA agrees that such information is difficult to obtain from the literature and therefore relied on written consultation with such experts in evaluating whether the three conditions proposed by the 2005 SAP had been met for a particular crop species.

In consulting with experts for a particular crop, EPA asked at least three individuals a series of questions designed to address the issues identified by the 2005 SAP as relevant for evaluating whether a PVCP-PIP would be low risk with respect to concerns associated with weediness if it were to be found in the particular species. Specifically, EPA wanted to know:

- Does this crop form viable hybrids in nature (i.e., without human intervention) with wild or weedy relatives in the United States (including Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa)?

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If yes, what species are they? Which of these species are themselves commercially grown crops? What is the frequency of hybrid production? Have hybrids demonstrated enhanced fitness (vigor) relative to parental varieties? Can the hybrids reproduce asexually? Are the hybrids sexually fertile?

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If hybrids are sexually fertile, will they outcross or only backcross with the crop parent? How does the phenology of the crop species compare with the phenology of plant(s) with which it is sexually compatible? Are there any other attributes of these species that may enhance or inhibit sexual reproduction and species out-crossing?

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• Is this crop known to become feral or easily spread into non-crop areas in the United States (including Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa)? If yes, have escaped plants formed reproducing and sustaining populations in non-crop areas? Where has this been known to happen? With what frequency is this likely to occur? Have feral populations required weed management activity?

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• How likely is it that this crop would become feral or easily spread into non-crop areas if it acquired transgenic resistance to one or more viruses? What is the basis for your answer?

EPA focused these questions on "non-crop areas" to emphasize that the key consideration is a crop's behavior in natural settings. EPA recognizes that most crops within agricultural fields form volunteer populations, where propagules of the crop from the previous rotation grow in the subsequent crop rotation. The Agency did not consider behavior in crop areas when evaluating the crops for inclusion on the list at proposed § 174.27(a)(1).

The responses to specific Agency-posed questions received from these expert consultations are available in the docket for this proposed rule (Ref. 42). EPA considered the experts' responses in conjunction with other information when determining whether to list a crop at proposed § 174.27(a)(1), as discussed below. Crops that EPA evaluated but did not include in the proposed list for one reason or another are discussed in Unit VII. where comment on these crops is specifically requested.

EPA notes that the 2005 SAP also suggested the Agency "consider the geographic distribution of crops and their wild relatives when considering potential exemptions" (Ref. 11). Although this is a potential option the Agency could pursue, a number of considerations limit the utility of using the potential for geographic isolation in determining whether a plant could be included on the list in § 174.27(a)(1). For example, EPA would need to consider carefully whether such isolation is likely to remain throughout the commercial life of the PVCP-PIP. Such isolation could occur if the crop containing the PVCP-PIP would not be commercially viable in the areas where wild relatives occur given biological considerations that are unlikely to change. However, geographic isolation could also be due to factors that may change throughout the commercial life of a PVCP-PIP, e.g., individual farmer choices of which crops to plant. Because of such considerations, EPA anticipates that it would only be able to support an exemption dependant on geographic restrictions where biological or similar factors provide assurance that the geographic isolation will remain constant during the entire commercial life of the PVCP-PIP.

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The next several Subunits summarize EPA's conclusions to include the crops listed at proposed § 174.27(a)(1) based on consideration of the conditions suggested by

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the 2005 SAP and their recommendation that evaluation of these conditions be done in consultation with breeders, agronomists, and ecologists familiar with the particular species. The analyses below indicate that there is an extremely low probability that virus resistance conferred through a PVCP-PIP in any of these plants would significantly alter existing plant population dynamics or existing ecological relationships. The list is straightforward, providing an easy-to-understand criterion. Accordingly, EPA is proposing that a developer may self-determine whether a PVCP-PIP meets this criterion, i.e., whether the plant containing the PVCP-PIP is on the proposed list, because no further data or information would be needed to evaluate whether ecological relationships could be disrupted through increased weediness when the plant modified to contain the PVCP-PIP is on the list.

a. *Anthurium.* EPA proposes that anthurium (*Anthurium* spp.) be included on the list in § 174.27(a)(1) based on EPA consultations with anthurium experts. These consultations indicate that anthurium meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make anthurium weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "The commercial species [of] *Anthurium* (*Anthurium schezerianum and Anthurium andraenum*) have been grown outdoors since the early 1900's in semi-tropical and tropical areas of the US and there are no records of any commercial species escaping and becoming feral into non-crop areas. There is no reason to believe that acquiring transgenic resistance to one or more viruses would increase the ability of plants to become feral or easily spread into non-crop areas" (Ref. 42). EPA therefore believes that anthurium meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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b. *Asparagus.* EPA proposes that asparagus (*Asparagus officinale*) be included on the list in § 174.27(a)(1) based on EPA consultations with asparagus experts. These consultations indicate that asparagus meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert said, "Although volunteer asparagus plants may grow "wild" (i.e., not intentionally cultivated), they are not typically considered to be weeds. There are several horticultural varieties of asparagus, which could potentially be cross-pollinated. However, considering that asparagus is insect pollinated, this is likely to occur only in the rare situation where an asparagus grower also is growing horticultural varieties" (Ref. 42). Second, the experts agreed that asparagus is not currently weedy or invasive outside of agricultural fields in the United States. Two of the three experts indicated that asparagus can infrequently become feral. However, "[a]sparagus is not typically considered to be a weedy species. In addition, since asparagus has separate male and female plants, it is considerably more difficult for "wild" populations to become established. Asparagus is also a relatively slow growing plant such that eradication (if necessary) would not be particularly onerous" (Ref. 42). Third, these experts agreed that it is unlikely that acquisition of virus resistance would make asparagus weedy or invasive. For example, one expert stated, "I have worked with this crop since 1978 and in all those years, I have not observed asparagus to become easily spread at all in non-crop

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or crop areas. Although asparagus does rarely grow wild in some areas (usually the temperate zones) asparagus is a very poor competitor with weeds and other plants and asparagus requires much attention and cultural care to thrive. I have only viewed a very rare occassionaly [sic] plant along fence rows and they usually are very weak and non-vigorous. Acquired transgenic resistance would do nothing to affect asparagus to become feral" (Ref. 42). EPA therefore believes that asparagus meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

c. *Avocado.* EPA proposes that avocado (*Persea americana*) be included on the list in § 174.27(a)(1) based on EPA consultations with avocado experts. These consultations indicate that avocado meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make avocado weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated "Transgenic resistance should not affect the likelihood of spread. Viral susceptibility is not an important factor limiting the plant's ability to become feral" (Ref. 42). EPA therefore believes that avocado meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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d. *Banana.* EPA proposes that banana (*Musa acuminata*) be included on the list in § 174.27(a)(1) based on EPA consultations with banana experts. These consultations indicate that banana meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make banana weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated "[i]t is highly unlikely that banana with acquired transgenic resistance would spread to non-crop areas because the probability of crossing is extremely small. Through vegetative propagation it will require man [sic] intervention just as non-transgenic plants" (Ref. 42). EPA therefore believes that banana meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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e. *Barley.* EPA proposes that barley (*Hordeum vulgare*) be included on the list in § 174.27(a)(1) based on EPA consultations with barley experts. These consultations indicate that barley meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make barley weedy or invasive, as viruses are not consistently associated with failure of barley to show any evidence of being weedy or invasive. Three experts contacted by EPA indicated agreement with these statements. For example, one expert stated that he believes the likelihood that barley would become feral or easily spread into non-crop areas if it acquired transgenic virus resistance is "negligible. Barley has been cultivated for decades in many U.S.

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environments, including environments that impose relatively mild disease pressure, particularly for viral diseases, such as the upper midwest and western states, and barley has not been able to establish itself in those regions as a feral species" (Ref. 42). EPA notes that the 2005 SAP indicated that "barley can hybridize with *Hordeum jubatum*, which is a weed in the USA" (Ref. 11). However, three barley breeders consulted about this specific issue did not agree that hybridization was likely to occur. One stated, "In relation to *Hordeum vulgare subsp. Vulgare* (cultivated barley) *Hordeum jubatum* is in the tertiary genepool. This means crossability is extremely difficult event under laboratory conditions" (Ref. 42). A study that attempted to cross barley with two wild relatives, *H. murinum* L. and *H. jubatum* L., found that no hybridization occurred, even under favorable greenhouse conditions with forced pollination (Ref. 43). EPA therefore believes that barley meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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f. *Bean.* EPA proposes that bean (*Phaseolus vulgaris*) be included on the list in § 174.27(a)(1) based on EPA consultations with bean experts. These consultations indicate that bean meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert mentioned that "[h]ybrids between Phaseolus vulgaris and Phaseolus acutifolius (tepary bean) are only achieved through extensive crossing and embryo rescue and thus is highly unlikely to occur in nature" (Ref. 42). Another expert said bean would "only – but rarely – hybridize with wild vulgaris (only where wild vulgaris occur, generally not in [the United States] & there are often biological barriers to such occurring" (Ref. 42). Second, these experts agreed that bean is not currently weedy or invasive in the United States. Third, these experts agreed that it is unlikely that acquisition of virus resistance would make bean weedy or invasive. For example, one expert stated, "Viruses generally do not prevent susceptible beans from making a crop (just the yield and quality of the crop is greatly reduced" (Ref. 42). EPA therefore believes that bean meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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g. *Cacao.* EPA proposes that cacao (*Theobroma cacao*) be included on the list in § 174.27(a)(1) based on EPA consultations with cacao experts. These consultations indicate that cacao meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make cacao weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated that "cacao is difficult to cultivate, the seeds are very susceptible to desiccation, and germination must occur within a few days or the seed die [sic]" (Ref. 42). EPA therefore believes that cacao meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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h. *Carnation.* EPA proposes that carnation (*Dianthus caryophyllus*) be included on the list in § 174.27(a)(1) based on EPA consultations with carnation experts. These consultations indicate that carnation meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can

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form viable hybrids in nature. Two, it is not currently weedy or invasive in the United States. One expert indicated that Arkansas and Massachusetts have populations of feral *Dianthus caryophyllus*. However these have not required management activity because "populations have remained small consisting of only a few plants" (Ref. 42). Three, there is no reason to believe that acquisition of virus resistance would make carnation weedy or invasive. One expert stated, "Most species of *Dianthus* are self-incompatible, and commercial selections of carnation require hand pollination, and set little viable seed. There is no record of carnation, *D. caryophyllus*, being naturalized or invasive in any part of the world" (Ref. 42). EPA therefore believes that carnation meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

i. *Chickpea.* EPA proposes that chickpea (*Cicer arietinum*) be included on the list in § 174.27(a)(1) based on EPA consultations with chickpea experts. These consultations indicate that chickpea meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make chickpea weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated that "there is no chance that chickpea would become feral with or without virus resistance. The susceptibility of the seeds to rotting without seed treatment would prevent any spread to non-crop areas. Resistance to viruses would not affect this outcome" (Ref. 42). EPA therefore believes that chickpea meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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j. *Citrus.* EPA proposes that citrus (*Citrus* spp.) be included on the list in § 174.27(a)(1) based on EPA consultations with citrus experts. These consultations indicate that citrus meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert mentioned that citrus can hybridize with other *Citrus* species and certain other closely related species in the sub-family Aurantioidea. However, this expert also noted that it was unlikely to hybridize naturally with any of these species that are found in the United States because they are not closely related and "would only be in the tertiary genepool for citrus" (Ref. 42). Another expert pointed out that Rangpur lime is sometimes mentioned as native to Florida, but he did not think this was true; as far as he knew, there are no wild or weedy relatives of citrus found in the United States. Second, these experts agreed that citrus is not currently weedy or invasive in the United States. One expert mentioned that there are "small feral populations of citrus found in Florida, mostly on the borders of the Everglades area and in some old forests…. However, these populations have not expanded their range. I know of no weed management efforts" (Ref. 42). Third, these experts agreed that it is unlikely that acquisition of virus resistance would make citrus weedy or invasive. For example, one expert stated that "citrus is simply not an aggressive grower with or without a virus" (Ref. 42). EPA therefore believes that *Citrus* species meet the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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k. *Coffee.* EPA proposes that coffee (*Coffea arabica* and *Coffea canephora*) be included on the list in § 174.27(a)(1) based on EPA consultations with coffee experts. These consultations indicate that both species of coffee meet the three conditions outlined above by the SAP: They do not have wild or weedy relatives in the United States with which they can form viable hybrids in nature, they are not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make coffee weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "Coffee plantations that are abandoned usually decay and are not overtaken by coffee plants. The crop needs maintenance to grow properly. It is not a weedy species" (Ref. 42). EPA therefore believes that coffee meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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l. *Corn.* EPA proposes that corn (maize; *Zea mays*) be included on the list in § 174.27(a)(1) based on EPA's extensive experience regulating PIPs in corn (Ref. 44), literature that is available on corn biology, the OECD Consensus Document on the Biology of *Zea mays* subsp. *mays* (Maize) (Ref. 45), and EPA consultations with corn experts (Ref. 42). OECD consensus documents are written by national experts who freely consult with breeders, agronomists, and ecologists who are specialists in the field. Each document must be reviewed and approved by experts in the 30 OECD member countries, and often by experts from non-OECD member countries. This body of information indicates that corn is low risk with respect to concerns associated with weediness.

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EPA's 2001 risk assessment for *Bt* PIPs evaluated the potential for corn to form viable hybrids with wild or weedy relatives in the United States (Ref. 44). EPA's summary conclusion was that while wild relatives of corn (i.e., Eastern Gama Grass and teosintes) may exist in the United States, there is no significant risk of gene capture and expression of a PIP in any of these relatives. The potential for pollen-directed gene flow from corn to Eastern Gama Grass is extremely remote. This is evidenced by the difficulty with which *Tripsacum dactyloides* x *Zea mays* hybrids are produced in structured breeding programs. Additionally, the genus does not represent any species considered as serious or pernicious weeds in the United States or its territories. Any introgression of genes into this species as a result of cross fertilization with genetically modified corn is not expected to result in a species that is weedy or difficult to control. In many instances where hybridization has been directed between these two species, the resultant genome is lacking in most or all of the corn chromosomal complement in subsequent generations. Many of the *Zea* species loosely referred to as "teosintes" will produce viable offspring when crossed with *Zea mays* ssp. mays. None of these plants are known to harbor weedy characteristics, and none of the native teosinte species, subspecies, or races are considered to be aggressive weeds in their native or introduced habitats. In fact, many are on the brink of extinction where they are indigenous and will be lost without human intervention (i.e., conservation measures). Two of the three experts EPA consulted indicated that corn will not form viable hybrids with any wild or weedy relatives in the United States. The third indicated that hybrids could be formed with teosintes, but that a hybrid "would lose its seed dispersal ability, so would have highly diminished ability to propagate in the wild. In regions where teosinte is a weed (mostly in Mexico), the

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teosintes have been naturally selected to have 'gametophyte factors' (e.g., *Ga1-s*, *Tcb1*), that essentially block corn pollen from fertilizing teosinte" (Ref. 42).

Further, the body of information and the experts that EPA consulted on corn indicate that it is not currently weedy or invasive in the United States. None of the landraces or cultivated lines of *Zea mays* are considered to have weedy potential, and all are generally considered to be incapable of survival in the wild as a result of breeding practices (i.e., selection) during domestication of the crop. According to the OECD consensus document, "[m]aize has lost the ability to survive in the wild due to its long process of domestication, and needs human intervention to disseminate its seed. Although corn from the previous crop year can overwinter and germinate the following year, it cannot persist as a weed" (Ref. 45). One expert EPA consulted stated, "Maize does not become feral or spread easily into non-crop areas in the United States or its territories. During its domestication many centuries ago, maize lost many of the attributes necessary to sustain itself in nature" (Ref. 42).

Finally, there is no reason to believe that acquisition of virus resistance would make corn weedy or invasive, as viruses are not consistently associated with failure of corn to show any evidence of being weedy or invasive. The experts EPA consulted agree that corn's becoming weedy with acquisition of a PVCP-PIP is unlikely. For example, one expert indicated, "Domesticated maize has no seed dispersal mechanism. Humans are required to remove kernels from the cob (a typical cob holds 500-1000 kernels, which would essentially try to all grow in the same spot, this would starve the resulting plants for nutrients and water and result in there being no progeny). Maize would essentially die out within a year or two, without human intervention" (Ref. 42). EPA therefore believes that corn meets the conditions recommended by the 2005 SAP for inclusion on the § 174.27(a)(1) list and will present low risk with respect to weediness.

m. *Cowpea*. EPA proposes that cowpea (black-eyed pea; *Vigna unguiculata*) be included on the list in § 174.27(a)(1) based on EPA consultations with cowpea experts. These consultations indicate that cowpea meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert indicated, "the cowpea is a highly self-pollinating crop that rarely outcrosses with other cowpeas. I expect that it might be possible for cowpea to rarely outcross with a 'wild' *V. unguiculata*, but it is probably safe to assume that the 'wild' cowpea genotypes don't exist in the United States" (Ref. 42). Second, the experts agreed that cowpea is not currently weedy or invasive outside of agricultural fields in the United States. One expert said, "I am not aware of any instance where the cowpea has become feral or easily spread into non-crop areas in the United States. HOWEVER, I am aware of instances where cultivated cowpea varieties have become weed pests in cultivated areas in the United States where OTHER CROPS are grown. For example, cowpea varieties with hard seeds can be a weed problem in soybean crops. The hard cowpea seeds over-winter in the soil and can produce plants in subsequent years; these cowpea plants often can't be easily killed by soybean herbicides (closely related plant) and the seeds are often so close in size to soybean seeds that [they] can be difficult to remove from the harvested soybean product" (Ref. 42). However, EPA considers that the key consideration is the plant's behavior in natural settings, including

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semi-managed habitat surrounding agricultural fields, as opposed to its behavior within the fields themselves. Third, these experts agreed that it is unlikely that acquisition of virus resistance would make cowpea weedy or invasive. For example, one expert stated "I am not aware of any virus problem in cowpea, if resolved via transgenic means, would result in the crop becoming feral" (Ref. 42). EPA therefore believes that cowpea meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

n. *Cucumber.* EPA proposes that cucumber (*Cucumis sativus*) be included on the list in § 174.27(a)(1) based on EPA consultations with cucumber experts. These consultations indicate that cucumber meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make cucumber weedy or invasive. The experts contacted by EPA indicated agreement with these statements. For example, one expert stated that "cucumber could not become feral due to acquired transgenic virus resistance. The failure for [cucumber] to survive without human intervention is not due to disease attack, but rather due to [its] ability to compete with native plants and weeds, and to withstand the stresses they are exposed to outside of cultivation, particularly drought" (Ref. 42). EPA therefore believes that cucumber meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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o. *Gerbera.* EPA proposes that gerbera (*Gerbera* spp.) be included on the list in § 174.27(a)(1) based on EPA consultations with gerbera experts. Two experts indicated that there are no wild or weedy relatives in the United States with which gerbera can form viable hybrids in nature. A third said, "*Gerbera jamesonii* Bolus ex Adlam has been recorded as naturalized in Florida. However, it is most likely *Gerbera hybrida* (*Gerbera jamesonii* x *G. viridiflora* Schultz-Bip) which is the designation for the commercially available *Gerberas*" (Ref. 42). Regarding the ferality of gerbera species, two experts believed feral populations were not known to occur, while a third noted, "Although *G. jamesonii* (or *G. hybrida*) is attributed to Florida, it is most likely a low risk for forming feral populations" (Ref. 42). All three experts believed it unlikely that acquired virus resistance could lead to gerbera becoming feral or easily spreading into non-crop areas. One expert said, "*Gerbera*, in general, is a short-lived perennial in the United States. It suffers from a number of fungal and bacteria pathogens. A transgenic virus-resistant *Gerbera* offers little in terms of [increased] fitness and increased invasive potential" (Ref. 42).

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p. *Gladiolus.* EPA proposes that gladiolus (*Gladiolus* spp.) be included on the list in § 174.27(a)(1) based on EPA consultations with gladiolus experts. These consultations indicate that gladiolus meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make gladiolus weedy or invasive. The experts contacted by EPA indicated agreement with these statements. For example, one expert said, "No gladiolus species or hybrid has ever been documented as having

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successfully naturalized in the United States. Virus resistance is not likely to make this any more likely" (Ref. 42). EPA therefore believes that gladiolus meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

q. *Lentil.* EPA proposes that lentil (*Lens culinaris*) be included on the list in § 174.27(a)(1) based on EPA consultations with lentil experts. Although lentil was not on the list of plants recommended by the 2004 SAP, several experts consulted about other crops mentioned that lentil also appeared to meet the criteria that EPA was investigating. Consultations about lentil indicate that it meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make lentil weedy or invasive. The experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "Lentil could not possibly survive in the wild on its own. [Lentils are] rather delicate plants, small in stature and very weak in competition for space or water. It needs great care from grower [sic] to produce seeds in cultivation. Its seed could not possibly survive in the wild due to rotting by soil-born microorganisms. Resistance to one or more viruses will not increase the survivability of lentil seeds in the wild" (Ref. 42). EPA therefore believes that lentil meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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r. *Mango.* EPA proposes that mango (*Mangifera indica*) be included on the list in § 174.27(a)(1) based on EPA consultations with mango experts. These consultations indicate that mango meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make mango weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "spread of mango seed by humans or animals into non-crop areas is rare and suitable environments are few. Transgenic resistance should not affect the likelihood of spread. Viral susceptibility is not an important factor limiting the plant's ability to become feral" (Ref. 42). EPA therefore believes that mango meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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s. *Orchids.* EPA proposes that all genera of orchids in the family Orchidaceae be included on the list in § 174.27(a)(1) based on EPA consultations with orchid experts. These consultations indicate that orchids meet the three conditions outlined above by the SAP: They do not have wild or weedy relatives in the United States with which they can form viable hybrids in nature, they are not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make orchids weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "Species within these genera have specific insect pollinators and those insects are unlikely [to] be present for pollination in United States. In addition, species within these genera are very difficult to grow from seed without human intervention, requiring a symbiotic relationship with a specific

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fungal species. Acquiring transgenic resistance to one or more viruses would not affect pollination or seed germination" (Ref. 42). EPA therefore believes that species in the orchid family meet the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

t. *Papaya.* EPA proposes that papaya (*Carica papaya*) be included on the list in § 174.27(a)(1) based on EPA consultations with papaya experts. These consultations indicate that papaya meets the three conditions outlined above by the SAP. First, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. Although *Carica papaya* has been successfully crossed with *Vasconellea* species using laboratory-based embryo rescue techniques, such hybrids do not form in nature (Ref. 42). Second, although all three breeding experts agreed that papaya is known to establish outside of agricultural areas through human- and animal-mediated seed dispersal, the species is not considered to be weedy or invasive. For example, one expert stated, "I have observed small feral [papaya] populations in Guam, Hawaii and Puerto Rico… in areas close to human dwellings and activities…. The feral papayas are not weedy and are nonaggressive, they can easily be removed by cutting down." Further, as stated in USDA-APHIS's response to a petition for determination of nonregulated status for transgenic virus-resistant papaya, "Papaya is not listed as a weed in the Federal Noxious Weed Act (7 U.S.C. 2801-2813) and is not reported by the Weed Society of America to be a common or troublesome weed anywhere in the United States (Bridges and Bauman, 1992; Holm et al. 1979; Muenscher, 1980)" (Ref. 46). Third, two of three experts indicate there is no reason to believe that acquisition of virus resistance would make papaya weedy or invasive. The third expert said that it was "[v]ery likely" papaya would become feral or easily spread into non-crop areas if it acquired transgenic resistance to one or more viruses because "[a]necdotal and informal reports at papaya conferences gave evidence that the virus resistance transgene was found in feral populations" (Ref. 42). However, this comment seems to reflect the fact, as noted above, that papaya does occasionally form feral populations in spite of not being weedy or aggressive, and this characteristic would be expected whether the papaya is transgenic or not. In his comments to EPA, another expert concludes by saying that territorial records show papaya was not a weed in Hawaii prior to the discovery of papaya viruses in the 1940s. If papaya was not considered a weed prior to exposure to viruses, then there is no reason to believe that a virus resistant papaya would become a weed. Another expert corroborates this conclusion by stating, "I see no competitive advantage of [virus-resistant] transgenic papayas over nontransgenic papayas…. Papaya requires high levels of human inputs to thrive or survive, including fertilizers, chemicals and care" (Ref. 42). EPA therefore believes that papaya meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

u. *Pea.* EPA proposes that pea (*Pisum sativum*) be included on the list in § 174.27(a)(1) based on EPA consultations with pea experts. These consultations indicate that pea meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make pea weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert

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stated, “pea is not likely to become feral or easily spread into non-crop areas due to acquired resistance to one or more viruses. Acquisition of transgenic viral resistance would not provide any adaptive advantage for survival of the transgenic crop plants. Peas have been produced in the US for more than 75 years with infrequent viral epidemics (5-9 year cycles) and no feral populations of pea have been recorded; therefore environmental and cultural conditions are the more likely agent preventing establishment of feral populations” (Ref. 42). EPA therefore believes that pea meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

v. *Peanut.* EPA proposes that peanut (*Arachis hypogaea*) be included on the list in § 174.27(a)(1) based on EPA consultations with peanut experts. These consultations indicate that peanut meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make peanut weedy or invasive. All three experts contacted by EPA indicated agreement with these statements. For example, one expert stated, “virus pressure is not the limiting factor. Even without virus pressure peanut (Arachis hypogaea) are not able to become feral or easily spread into non-crop areas. Peanut are not able to sustain long term natural populations without cultivation by man” (Ref. 42). EPA therefore believes that peanut meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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w. *Pineapple.* EPA proposes that pineapple (*Ananas comosus*) be included on the list in § 174.27(a)(1) based on EPA consultations with pineapple experts. These consultations indicate that pineapple meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert indicated, “The taxonomy of the genus Ananas was recently critically reviewed and revised (Chan et al., 2003) and all of the wild relatives of pineapple are classified in the same genus and species as the cultivated pineapple but are different botanical varieties. These are Ananas comosus var. ananassoides and A. comosus var. parguazensis (Chan et al., 2003). If these wild relatives are found in the United States and its territories they would be in cultivated gardens or in pots. There are no reports that A. comosus var comosus or its wild relatives survive naturally in the wild or pose a potential threat as weed species. If natural crosses between Ananas species occur in nature, it is highly unlikely that seed produced from them would survive to produce a mature plant” (Refs. 42 and 47). Second, the experts agreed that pineapple is not currently weedy or invasive in the United States. Third, these experts agreed that it is unlikely that acquisition of virus resistance would make pineapple weedy or invasive. For example, one expert stated, “Assuming transgenic plants were resistant to all known pests, pineapple still cannot compete with weeds, which quickly overtop slower growing pineapple plants. Pineapple lacks any natural mechanism for vegetative propagation and does not propagate naturally by seeds because seedlings are delicate and require special care to survive to maturity” (Ref. 42). EPA therefore believes that pineapple meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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x. *Potato.* EPA proposes that potato (*Solanum tuberosum*) be included on the list in § 174.27(a)(1) based on the Agency's experience regulating PIPs in potato (Ref. 44), literature that is available on potato biology, the OECD Consensus Document on the Biology of *Solanum tuberosum* subsp. *tuberosum* (Potato) (Ref. 48), and EPA consultations with potato experts (Ref. 42). This body of information indicates that potato is low risk with respect to concerns associated with weediness.

EPA's 2001 risk assessment for *Bt* PIPs evaluated the potential for potato to form viable hybrids with wild or weedy relatives in the United States (Ref. 44). EPA's conclusion was that there is no foreseeable risk of gene capture and PIP expression in wild relatives of *Solanum tuberosum* in the United States. Successful gene introgression into tuber-bearing *Solanum* species is virtually excluded due to constraints of geographical isolation and other biological barriers to natural hybridization (Ref. 49). These barriers include incompatible (unequal) endosperm balance numbers that lead to endosperm failure and embryo abortion, multiple ploidy levels, and incompatibility mechanisms that do not express reciprocal genes to allow fertilization to proceed. No natural hybrids have been observed between these species and cultivated potatoes in the United States.

The body of information EPA consulted on potato also indicates that the crop is not currently weedy or invasive in the United States. According to the OECD consensus document, "[o]utside the field, potato seedlings will have difficulty establishing themselves as they cannot compete with other plants. Love et al., 1994 report that these seedlings are limited to cultivated areas for reasons of competition and adaptation. Potato tubers can be spread during transportation and use, but generally these plants will not be established for a long time due to unfavourable environmental conditions. In general, the potato is not known as a coloniser of unmanaged ecosystems" (Ref. 48). One expert EPA consulted indicated potato "is a rare weed in potato plots but it never becomes feral in the United States" (Ref. 42).

Finally, there is no reason to believe that acquisition of virus resistance would make potato weedy or invasive, as viruses are not consistently associated with failure of potato to show any evidence of being weedy or invasive. The experts that EPA consulted agree that it is not very likely that potato would become feral or easily spread into non-crop areas if it acquired transgenic virus resistance. For example, one expert consulted indicated that "[t]he basis of poor survival of cultivars in natural habitats is not due to virus susceptibility" (Ref. 42). EPA therefore believes that potato meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

y. *Soybean.* EPA proposes that soybean (*Glycine max*) be included on the list in § 174.27(a)(1) based on literature that is available on soybean biology, the OECD Consensus Document on the Biology of *Glycine max* (L.) Merr. (Soybean) (Ref. 50), and EPA consultations with soybean experts. This body of information indicates that soybean meets the three conditions outlined above by the SAP: It does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make soybean weedy or invasive, as viruses are not

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consistently associated with failure of soybean to show any evidence of being weedy or invasive. All four experts contacted by EPA indicated agreement with these statements. For example, one expert stated, "Acquiring transgenic virus resistance will not change the ability of soybean to become feral since it will still be a domesticated species and does not have the attributes to survive without human intervention. Virus diseases in the U.S. do not generally cause major yield loses [sic] and resistance to some viruses is very common in soybean. Transgenic virus resistance will not substantially change how the soybean interacts with most environments" (Ref. 42). According to the OECD consensus document, "[t]he soybean plant is not weedy in character. In North America, *Glycine max* is not found outside of cultivation. In managed ecosystems, soybean does not effectively compete with other cultivated plants or primary colonizers" (Ref. 50). EPA therefore believes that soybean meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

z. *Starfruit.* EPA proposes that starfruit (*Averrhoa carambola*) be included on the list in § 174.27(a)(1) based on EPA consultations with starfruit experts. These consultations indicate that starfruit meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. One expert mentioned that starfruit can hybridize with wild *Averrhoa carambola*, but another expert indicated that researchers have concluded wild starfruit trees can no longer be found in the United States (Ref. 42). Second, these experts agreed that starfruit is not currently weedy or invasive in the United States. Third, these experts agreed that it is unlikely that acquisition of virus resistance would make starfruit weedy or invasive. For example, one expert stated, "It is highly unlikely that starfruit with acquired transgenic resistance would spread to non-crop areas because… seed recalcitrance in starfruit… results in a loss of viability shortly after harvest" (Ref. 42). EPA therefore believes that starfruit meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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aa. *Sugarcane.* EPA proposes that sugarcane (*Saccharum officinarum*) be included on the list in § 174.27(a)(1) based on EPA consultations with sugarcane experts. These consultations indicate that sugarcane meets the three conditions outlined above by the SAP. One, it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature. According to one expert, "Although in theory it should happen in more tropical regions of the world, hybrid seedlings among commercial or wild relatives are not observed. Breeders routinely generate hybrids among commercial sugarcane (derived from interspecific hybrids of *Saccarhum* [sic] *officinarum* and *S. sponteneum*), and among commercial and wild relatives (*S. spontaneum* mostly) under controlled conditions of heating and photoperiod control. The resulting progeny are quite weak and must be husbanded under greenhouse-type conditions prior to planting in the field" (Ref. 42). Second, these experts agreed that sugarcane is not currently weedy or invasive in the United States. One expert stated, "Commercial sugarcane is clonally propagated. Occasionally some of the harvested cane may be lost from the trucks or wagons while in transport from the field to the processing factory. If the cane has not been burned prior to harvest, volunteer plants occasionally grow along the transport route. This cane is not sexually reproducing, nor is it invasive in nature. Simple roadside mowing or natural weather conditions usually eliminate it" (Ref. 42). Third, these experts

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agreed that it is unlikely that acquisition of virus resistance would make sugarcane weedy or invasive. For example, one expert stated, "commercial sugar does not become a feral pest under regular commercial production conditions. The majority of existing commercial cultivars have been bred for genetic resistance to various disease-causing sugarcane viruses. None of these cultivars have become feral or a pest in anyway [sic]" (Ref. 42). EPA therefore believes that sugarcane meets the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

bb. *Tulips.* EPA proposes that tulips (*Tulipa* spp.) be included on the list in § 174.27(a)(1) based on EPA consultations with tulip experts. These consultations indicate that tulips meet the three conditions outlined above by the SAP. One, they do not have wild or weedy relatives in the United States with which they can form viable hybrids in nature. Two, they are not currently weedy or invasive in the United States, although two experts indicated that *Tulipa sylvestris* naturalizes in certain areas without being viewed as a significant problem because it reproduces only vegetatively. Three, there is no reason to believe that acquisition of virus resistance would make tulips weedy or invasive. One expert noted that this was "possible, but unlikely. Virus resistance could conceivably increase the vigor of the vegetative spread of *T. sylvestris*" (Ref. 42). However, three other experts believed that this was highly unlikely to occur. One said, "The need for chilling in this genus means that it is restricted to temperate areas with summer-cool climates. Areas where it can persist are very limited and there is a high degree of browsing of this genus by vertebrates such as deer that make seed production in the wild a very rare occurrence in nature in the U.S." (Ref. 42). EPA therefore believes that tulips meet the conditions recommended by the 2005 SAP for inclusion on the list and will present low risk with respect to weediness.

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ii. *Adding plants to the categorical exemption criterion in §174.27(a)(1).* As the Agency gains additional experience, it may propose to add crops to the list. In addition, any person may petition the Agency to add particular crops to the list. EPA would evaluate any potential candidates against the same considerations used in this rulemaking to develop the list in § 174.27(a)(1) discussed above. Consequently, for a petition to be successful, it should contain sufficient data or other information to allow EPA to perform such an analysis, e.g., published information or a consensus opinion among experts in the particular crop that addresses the questions EPA posed in its expert consultations (discussed in Unit III.C.2.i.). Petitioners are welcome to consult with EPA prior to preparing a submission to discuss the information that would be required. EPA would consult with USDA in evaluating petitions for adding plants to § 174.27(a)(1).

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Any subsequent addition of crops to the list in § 174.27(a)(1), either through the Agency's own initiative or in response to a petition from the public, may only occur through rulemaking. Under FIFRA section 25, rulemaking involves several steps, including reviews by the SAP and USDA. In general, EPA would seek to expedite the process and proceed through direct final rulemaking where feasible. Under such a process, in cases where EPA believes that the proposal will not raise scientifically complicated issues, EPA would simultaneously issue a final rule and a proposal. If no adverse comments were received, the final rule would go into effect and EPA would withdraw the proposed rule. In the event of adverse comment, EPA would withdraw the

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final rule and would proceed to issue a final rule that addressed the public comments received on the proposal. In addition, as part of this current rulemaking, because EPA's analysis to determine whether to add a crop to the list would be consistent with the criteria provided by the SAP, the Agency would request that the SAP generally waive its review of subsequent rules seeking to add further crops to the list in § 174.27(a)(1) unless EPA subsequently determines that a particular rule raised novel or particularly complex scientific issues.

iii. *Proposed exemption criterion conditional on Agency determination in § 174.27(a)(2)*. EPA recognizes that many PVCP-PIP/plant combinations would reasonably be expected to pose low risk with respect to weediness even though the crop plant containing the PVCP-PIP is not on the Agency's proposed list in § 174.27(a)(1). EPA has not conducted an exhaustive survey of all crop plants to evaluate them for inclusion on this list and therefore recognizes that additional plants may meet the conditions that were used to compile this list of plants. Therefore, in addition to the categorical exemption criterion, EPA also believes that a criterion conditional on Agency determination could be developed that would identify plants that are low risk with respect to weediness.

EPA is considering four options for such a conditional exemption criterion under which PVCP-PIP/plant combinations that fail to meet § 174.27(a)(1) could still meet § 174.27(a) under § 174.27(a)(2), subject to an Agency review. Each of the options reflects a somewhat different approach to implementing the recommendations of the 2005 SAP (Ref. 11). EPA does not currently have a preferred approach and presents several options to promote full consideration of the issues, although option 1 is presented in the regulatory text so the public could see how § 174.27(a)(2) might fit into the overall framework of the exemption.

a. *Option 1.* The first option for § 174.27(a)(2) provides the strictest interpretation of the 2005 SAP advice. Under this option, a PVCP-PIP would meet § 174.27(a) under § 174.27(a)(2) if the Agency determines after review that the plant containing the PIP meets all of the following:

(i) Has no wild or weedy relatives in the United States with which it can form viable hybrids in nature.

(ii) Is not a weedy or invasive species outside of agricultural fields in the United States.

(iii) Is unlikely to establish weedy or invasive populations outside of agricultural fields in the United States even if the plant contains a PVCP-PIP.

EPA would expect exemption submissions to document that the plant meets these conditions in the opinion of agronomists, breeders, ecologists, and other experts working with the specific taxa in question or based on data. When these conditions are met, the likelihood that a PVCP-PIP could cause increased weediness of any plant would be very small, as discussed in the following paragraphs.

If the plant containing the PVCP-PIP has no wild or weedy relatives in the United States with which it can form viable hybrids in nature and thus would meet the criterion in § 174.27(a)(2)(i) under option 1, it would not be possible for the PVCP-PIP to inadvertently be transferred to any wild or weedy relatives, e.g., through pollen flow.

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Whether the recipient plant "can produce viable hybrids in nature" is a critical attribute that would definitively determine the potential for introgression of the PVCP-PIP into a native or naturalized plant population. Although hybrids must be able to reproduce themselves in order for introgression to occur, the production of "viable" hybrids (i.e., those that are able to grow) may be described more clearly in a regulatory standard than examining the reproductive potential of any hybrids. In many cases, reproductive potential of hybrids has not been fully investigated. Given that reduced fertility in F1 crop-wild hybrids is frequently restored to normal in subsequent generations (Ref. 37), measurement of hybrid fertility involves consideration of several generations. In addition, viability is a more reliable standard because even very low rates of gene transfer could lead to introgression (Ref. 51), suggesting that any degree of hybrid fertility could indicate the potential for introgression to occur. As noted by the 2005 SAP, "it is known that favorable alleles (including, perhaps, a PVCP-PIP) can pass easily from one species to another through hybrid zones, even when the hybrids have very low fitness (Barton 1986)" (Refs. 11 and 52). The Agency recognizes that introgression of a trait such as virus resistance into natural plant populations does not automatically confer a competitive advantage to the recipient population. However, at this time, there is little information available to predict categorically whether acquisition of such a trait might affect the competitiveness of a specific plant population, and the available information does not allow the Agency to make this determination *a priori*. The ability to produce viable hybrids is relatively easy to evaluate, resulting in a clear criterion that ensures an effective limitation on the potential for introgression. Such language also clarifies that the relevant question is whether the hybrid can be produced "in nature." The fact that plants could be crossed in the laboratory or greenhouse is not necessarily indicative of a plant's true reproductive potential. The Agency's focus is whether a viable hybrid could be produced under normal growing conditions in the field or in nature, rather than under controlled experimental conditions that might have little relevance to behavior in the environment.

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If the plant containing the PVCP-PIP is not a weedy or invasive species outside of agricultural fields in the United States and thus would meet the criterion in § 174.27(a)(2)(ii) under option 1, established and persistent feral populations of the crop presenting difficult management issues in natural or semi-managed ecosystems would be unlikely. Thus, transfer of the PVCP-PIP from the crop to a feral population would be unlikely to exacerbate what could already be a difficult problem by inadvertently increasing the population's weediness potential. EPA proposes inclusion of the term "outside of agricultural fields" to emphasize that the key consideration is the plant's behavior in natural settings, including semi-managed habitat surrounding agricultural fields as opposed to its behavior within the fields themselves. EPA recognizes that most crops within agricultural fields form volunteer populations, where propagules of the crop from the previous rotation grow in the subsequent crop rotation. The Agency believes the language "outside of agricultural fields" appropriately excludes this situation from consideration.

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If the plant containing the PVCP-PIP is unlikely to establish weedy or invasive populations outside of agricultural fields in the United States even if the plant contains a PVCP-PIP and thus would meet the criterion in § 174.27(a)(2)(iii) under option 1, an

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additional level of assurance would be provided that the crop plant would not present weediness concerns through acquisition of a PVCP-PIP. EPA believes that this condition could in general be met based on the opinion of experts on the particular crop. Experts may judge, for example, that acquisition of virus resistance is unlikely to change the weedy or invasive characteristics of the plant if the crop does not appear to be weedy or invasive when virus infection is known to be absent from a particular area or over a particular period of time. Available empirical data could be used in the determination or may be gathered if expert opinion cannot resolve the question.

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EPA proposes to define the term "weedy species" used in § 174.27(a)(2)(ii) to mean "a species that is an aggressive competitor in natural ecosystems." EPA intends to use the term "invasive species" consistent with the definition in Executive Order 13112, meaning an alien species whose introduction causes or is likely to cause economic or environmental harm or harm to human health. An alien species means, with respect to a particular ecosystem, any species, including its seeds, eggs, spores, or other biological material capable of propagating that species, that is not native to that ecosystem. EPA uses the phrase "weedy or invasive populations" in § 174.27(a)(2)(iii) consistent with these definitions.

EPA notes that the criterion in § 174.27(a)(2)(i) under option 1 does not necessarily strictly hold for every crop that appears on the list in proposed § 174.27(a)(1). In some cases, EPA was able to make a low risk determination for a particular crop, e.g., corn, in spite of the possible presence of wild or weedy relatives in the United States with which the plant may in rare cases form viable hybrids in nature. EPA has presented the basis for such conclusions in this proposed rule, and the public can clearly understand why the crops in § 174.27(a)(1) meet the Agency's low risk standard with respect to weediness concerns. Given that several crops for which EPA has made a low risk determination and proposes to include in § 174.27(a)(1) would not meet § 174.27(a)(2) as proposed under option 1, EPA believes that option 1 may be too narrow. Accordingly, EPA is considering other options for § 174.27(a)(2) that are based on a less literal interpretation of the SAP's recommendations but which the Agency believes are nevertheless consistent with the SAP's intent.

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b. *Option 2.* The second option EPA is considering is that a PVCP-PIP would meet the criterion in § 174.27(a)(2)(i) if "the plant containing the PIP has no wild or weedy relatives in the United States with which it can form viable, *fertile* hybrids in nature, or if fertile, the resulting hybrid cannot establish populations in the environment." EPA is considering this option because most crops are able to form viable hybrids with a wild or weedy relative in some part of the United States. However, some viable, fertile hybrids may nevertheless present low risk with respect to concerns associated with weediness, e.g., if the hybrids are weak and lack the ability to establish. On the other hand, fertility and the potential to establish are more difficult characteristics to evaluate than viability because many more variables affect the determination, suggesting that it might be more appropriate in these cases for the Agency to require that data be collected for a period of time after commercial deployment that could confirm the Agency's original analysis. However, while such conditions may be readily placed on a PVCP-PIP registration, they could not be placed on an exempt PVCP-PIP. In addition,

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determinations under option 2 would be more difficult for the public to predict than determinations under option 1, as discussed in Unit III.A.2.

c. *Option 3.* Under the third option being considered, EPA would adopt only the criteria in § 174.27(a)(2)(i) and (a)(2)(ii) as discussed above under option 1. The rationale for such an approach is that it may not be necessary to evaluate the criterion in § 174.27(a)(2)(iii) in order to make a low risk determination because the issues are adequately addressed by the other two criteria. Viruses generally do not uniformly affect crops every season in every place they are planted – even those crops that viruses significantly impact such that development of a PVCP-PIP to combat the disease might be undertaken. Crops will thus have repeated opportunity to escape cultivation in seasons and in areas where there is no virus infestation. If weedy tendencies are rarely or never observed in any part of the crop's range, it is unlikely that virus resistance affects the crop's ability to escape cultivation and establish weedy populations. Unlike wild or weedy plant relatives that may at times be infected by viruses and may be negatively impacted by viruses in ways that are not obvious to untrained observers, breeders and farmers are intimately aware of the type of damage done by virus infection to crops and are therefore well aware when their fields are or are not infected. Crop plants have been observed under a diverse range of environmental conditions over many years. If a PVCP-PIP were likely to make a crop weedy or invasive, such tendencies would likely have been observed even without virus resistance at some point in time given the level of observation crops generally receive due to the necessity to actively manage their cultivation. Such crops showing weedy or invasive tendencies would not meet the criterion in § 174.27(a)(2)(ii), suggesting that the criterion in § 174.27(a)(2)(iii) is largely redundant with this condition.

EPA notes that option 3 is likely to be equally as narrow as options 1 and 2. The advantage of the option would be a simplification of the issues that a PVCP-PIP developer would need to address as part of a submission for an exemption determination.

EPA could consider factors that are not considered under options 1-3 but that would affect the potential impact of PVCP-PIP acquisition as part of evaluating a PVCP-PIP for FIFRA registration. For example, EPA could take into account the effect of virus infection on such species, the existence and impact of any natural virus resistance in the population, the overlap of the plant's distribution with crop cultivation areas, and other relevant considerations.

d. *Option 4.* The fourth option EPA is considering is that a PVCP-PIP would meet § 174.27(a)(2) if the Agency determines that "the PVCP-PIP is unlikely to significantly change the population size or distribution of the species containing the PVCP-PIP outside of agricultural fields or the population size or distribution of any wild or weedy species in the United States that could acquire the PVCP-PIP through gene transfer." EPA is considering this fourth option because the Agency recognizes that many PVCP-PIPs excluded from exemption under the criterion in § 174.27(a)(2)(i) of options 1-3 because of wild or weedy relatives in the United States may nevertheless present low risk. The presence of wild or weedy relatives relates only to potential exposure of the PVCP-PIP and does not indicate whether the PVCP-PIP is likely to cause any adverse effects even if it were to transfer to these relatives. EPA believes that such an evaluation would be

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consistent with the advice of the 2005 SAP, which noted that "[t]he probability that a particular transgene will lead to increased weediness depends on the phenotype conferred by the transgene and on the ecological factor(s) currently limiting the size or distribution of the wild species. In particular, if the transgene alters plant response to an ecological factor limiting population size, then population dynamics may be affected. For PVCP-PIPs, the relevant consideration is whether virus resistance (conferred by the PVCP-PIP) leads to changes in the size or distribution of wild plant species with the PVCP-PIP" (Ref. 11).

With option 4, EPA would conduct a risk assessment to evaluate a clear end point – whether there is likely to be a significant change in the population size or distribution of the species containing the PVCP-PIP outside of agricultural fields or the population size or distribution of any wild or weedy species in the United States that could acquire the PVCP-PIP through gene transfer. However, for the vast majority of species, many characteristics that would influence this determination are currently poorly understood, e.g., the impact of virus infection on wild plant populations and the likely selective advantage afforded by acquisition of virus resistance. As a result, both the nature of EPA's evaluation and the type and extent of data that might need to be provided to the Agency resemble much more closely what would be required to evaluate weediness issues during a FIFRA registration review. In addition, the more the exemption determination process resembles a full risk assessment, the longer the time required for EPA to complete such a review.

Although EPA would seek public comment on determinations that a PVCP-PIP met § 174.27(a)(2) according to the procedure for exemptions utilizing any Agency-determined criteria, Agency determinations may be more controversial with this option than with other options that have more clearly defined criteria. EPA believes that case-by-case determinations could be made appropriately and that the data requirements needed to evaluate the criterion under option 4 would not necessarily be overly burdensome. EPA notes that in many cases much of the data, if not all, needed for EPA to evaluate a criterion such as this fourth option would also be needed for a petition for determination of nonregulated status submitted to USDA. EPA believes that the flexibility of this option will make it more likely that the Agency would identify the largest number of low risk products that could qualify for exemption.

For all options for proposed § 174.27(a)(2), the Agency believes the entire United States is the relevant scope of inquiry because the proposed exemption would carry no limitations on where the exempted PVCP-PIP/plant combination could be planted and thus could be planted in all areas subject to U.S. law. FIFRA section 2(aa) defines "State" as "a State, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa. Accordingly, the term "United States" used in this proposal includes all these areas, and EPA proposes to incorporate a definition of "United States" paralleling the FIFRA definition of "State" into the definitions in 40 CFR 174.3.

As an alternative to Agency review pursuant to § 174.27(a)(2), a developer could petition EPA to add a crop to the list in § 174.27(a)(1). In some cases, EPA expects that the same data/information that would support a determination that a crop meets §

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174.27(a)(2) would support listing the crop in § 174.27(a)(1). However, because a plant can only be added to the list in § 174.27(a)(1) through rulemaking, EPA expects that many developers will instead prefer to obtain an Agency determination under § 174.27(a)(2). However, once a plant is added to the list in § 174.27(a)(1), future PVCP-PIPs used in that plant would meet § 174.27(a) without any Agency review.

3. *Historical approaches.* In 1994 EPA proposed two different alternatives for exempting PVCP-PIPs from FIFRA requirements. The Agency prefers the approaches discussed in the preceding Subunit because they have been developed based on recent interactions with the SAP and thus represent the most current science. One 1994 alternative contained exemption criteria directed towards addressing concerns associated with gene transfer to identify those PVCP-PIP/plant combinations with the lowest potential to confer selective advantage on wild or weedy plant relatives. EPA described this alternative exemption as follows:

Coat proteins from plant viruses [would be exempt] if the genetic material necessary to produce a coat protein is introduced into a plant's genome and the plant has at least one of the following characteristics:

(1) The plant has no wild relatives in the United States with which it can successfully exchange genetic material, i.e., corn, tomato, potato, soybean, or any other plant species that EPA has determined has no sexually compatible wild relatives in the United States.

(2) It has been demonstrated to EPA that the plant is incapable of successful genetic exchange with any existing wild relatives (e.g., through male sterility, self-pollination).

(3) If the plant can successfully exchange genetic material with wild relatives, it has been empirically demonstrated to EPA that existing wild relatives are resistant or tolerant to the virus from which the coat protein is derived or that no selective pressure is exerted by the virus in natural populations (59 FR 60504, November 23, 1994).

EPA carefully reconsidered this 1994 proposal in its deliberations for today's proposed exemption and presented these criteria in modified form to the FIFRA SAP at the October 2004 and December 2005 meetings for consideration. In light of comments received from the FIFRA SAP and additional scientific information available since 1994, EPA no longer believes this alternative would adequately address questions associated with weediness in a manner that could be reasonably implemented. However, EPA still considers that it would be appropriate to limit the exemption based on the concerns outlined in the earlier proposal associated with acquisition of virus resistance through hybridization with a transgenic plant containing a PVCP-PIP.

Although similar in intent to characteristic (1) of this option proposed in 1994, today's proposed criterion in § 174.27(a)(2)(i) under option 1 focuses in part on the potential to "form viable hybrids in nature" rather than simply "exchange genetic material" because the former is a clearer standard for determining whether a PVCP-PIP could have the potential to affect a recipient plant population negatively. The ability to exchange genetic material, which is often demonstrated by performing hand crosses in the laboratory or greenhouse, may not indicate any relevant information about how the plants would behave in nature. Today's proposed criterion in § 174.27(a)(1) also uses a somewhat different list of plants than the four in the 1994 proposal. Several species have been added (see Unit III.C.2.i.) and tomato has been removed from the list because of information acquired through expert consultation. (See Unit VII. for a discussion of this

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information and to read EPA's request for comment). When EPA presented a criterion similar to the first characteristic in the 1994 proposal to the 2004 SAP, they responded that "the Panel was of the opinion that the absence of a competent wild/weedy relative positioned in relation to the plant containing the PVCP-PIP was an appropriate condition." The 2005 SAP also "was supportive of the Agency's intent to exempt from regulation any PVCP-PIP crops that (1) do not have sexually compatible wild relatives in the location of intended cultivation (US & Territories) and (2) are not likely to become weedy themselves" (Ref. 11).

EPA now also believes that characteristic (2) of the option proposed in 1994 may be insufficient based on the conclusions of the 2004 SAP and the National Research Council that current methods of bioconfinement are imperfect and are unlikely to adequately restrict gene flow (Refs. 25 and 53). The Agency asked the 2004 SAP whether the condition that "genetic exchange between the plant into which the PVCP-PIP has been inserted and any existing wild or weedy relatives is substantially reduced by modifying the plant with a scientifically documented method, (e.g., through male sterility)" would be necessary and/or sufficient to minimize the potential for a PVCP-PIP to harm the environment through gene transfer from the crop plant containing the PVCP-PIP to wild or weedy relatives. The Panel "accepted that tactics aiming at diminished gene exchange are highly desirable and even necessary but are not sufficient" (Ref. 25).

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In spite of such concerns, EPA is still considering whether a criterion involving biocontainment could be sufficient to enable the Agency to determine with review that a product presents low risk with respect to concerns associated with weediness. The 2005 SAP concluded "that if highly effective biological containment and biological mitigation methods could be deployed concurrently with the PVCP-PIP, then it would be possible to exempt crops with sexually compatible wild relatives. This opinion is different from the opinion of the October 2004 FIFRA SAP. The [2005] Panel concluded that this difference is probably due to advances in containment and mitigation strategies. For this reason, exemptions might be granted to any crop that hybridizes with a wild relative in the US, its possessions or territories, if the $F_1$ and BC (backcross) hybrids have very low fitness such that it is effectively lethal. Additionally, an exemption might be possible if specific genes for lowering fitness are in tandem constructs with the PVCP-PIP gene in such a way that they cannot readily segregate from each other. The Panel did not determine what level of effectiveness would be required but, it was agreed that stacked strategies would reduce the cumulative risk, and should be strongly considered" (Ref. 11).

Bioconfinement strategies are known to have a wide range of efficacy, and no standard level of efficacy to ensure environmental safety has been determined (Ref. 53). Additionally, some techniques may introduce risk concerns that must be evaluated, e.g., unintended impacts on wildlife that eat seeds or pollen (Ref. 25). However, scientific advancements may make bioconfinement techniques sufficiently reliable and safe in the future such that deployment with a PVCP-PIP would be sufficient to reach a low risk finding with respect to concerns associated with weediness (Refs. 54 and 55). Therefore, EPA is still considering a condition such as characteristic (2) proposed in 1994 that

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would constitute an alternative way to meet § 174.27(a)(2) under any of the options discussed in this Preamble. For example, § 174.27(a)(2) might read:

The Agency determines after review that the plant containing the PIP:

(i) Has no wild or weedy relatives in the United States with which it can form viable hybrids in nature or employs a highly effective biological containment technique.

(ii) Is not a weedy or invasive species outside of agricultural fields in the United States or employs a highly effect biomitigation construct that ensures escapes from cultivation are too unfit to compete with wild-types.

EPA believes that characteristic (3) of the option proposed in 1994 is sound conceptually. However, the Agency's intent in developing this exemption has historically been to have criteria that identify low risk PVCP-PIPs such that the criteria could be evaluated with information that a developer is likely to have acquired in the course of developing the product and not require significant data generation. The Agency presented a similar criterion to the 2004 SAP for their consideration: "all existing wild or weedy relatives in the United States with which the plant can produce a viable hybrid are tolerant or resistant to the virus from which the coat protein is derived." The Panel members suggested that such a criterion would be difficult to implement in a clear and transparent exemption review process given that "[t]he Panel had particular difficulty when attempting to add precision to approaches that should be followed when sampling wild and weedy relatives for the occurrence of specific virus tolerance or resistance as specified by the Agency."

As an alternative to a criterion like that described by characteristic (3) in the 1994 proposal whose evaluation would necessitate collection of potentially significant amounts of data, EPA presented another option to the 2005 SAP: "(i) the plant containing the PVCP-PIP is itself not a weedy or invasive species outside of agricultural fields in the United States, its possessions, or territories, and (ii) the plant containing the PVCP-PIP does not have relatives outside of agricultural fields in the United States, its possessions, or territories that are weedy or invasive species or endangered/threatened species with which it can produce viable hybrids in nature" (Ref. 11). However, the Panel concluded that "the probability that a particular transgene alters the dynamics of a wild relative cannot be predicted by the current status of the wild species as weedy, invasive, or threatened/endangered. The Panel agreed that the criteria proposed by the Agency would not correctly identify PVCP-PIPs which pose unacceptable environmental risks" (Ref. 11). EPA has therefore concluded that the Agency is unable at this time to articulate a clear criterion for exemption that would expand the eligible plants beyond those roughly described by the ideas in the 1994 characteristic (1) unless the Agency were to adopt a criterion whose evaluation involved conducting a risk assessment of the PVCP-PIP/plant combination such as it put forth in this preamble as the fourth option for proposed § 174.27(a)(2), i.e., that the PVCP-PIP is unlikely to significantly change the population size or distribution of the species containing the PVCP-PIP outside of agricultural fields or the population size or distribution of any wild or weedy species in the United States that could acquire the PVCP-PIP through gene transfer (discussed in Unit III.C.2.iii.d.).

The other alternative proposed in 1994 did not contain a criterion addressing concerns associated with gene flow. This option proposed a full categorical exemption

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for all PVCP-PIPs (59 FR 60503). This option is no longer the Agency's preferred approach for a number of reasons. Specifically, EPA has received scientific advice since issuance of the 1994 proposal calling into question the Agency's 1994 rationale that all PVCP-PIPs meet the FIFRA 25(b)(2) exemption standard, including gene flow considerations. Although EPA believes that many PVCP-PIPs present low risk and thus meet the FIFRA 25(b)(2) exemption standard, in order to categorically exempt all PVCP-PIPs, the Agency must be able to draw this conclusion for all PVCP-PIPs. Advances in scientific understanding since 1994 suggest it may not be possible to support this rationale for all PVCP-PIPs and that certain PVCP-PIPs may pose a greater level of risk than is characteristic of the group as a whole. For example, virus resistance is common in natural plant populations as evidenced by conventionally bred virus resistant plants that are only possible due to naturally existing resistance in crop and wild relative populations (Ref. 20). This fact suggests that acquisition of virus resistance is often unlikely to introduce a novel trait into many plant populations. However, some notable exceptions to the ubiquity of virus resistance in natural plant populations exist including the lack of successful conventionally bred resistance to barley yellow dwarf virus in major crops and the lack of natural resistance in some wild relatives of these crops (Ref. 36). Such information suggests that acquisition of a PVCP-PIP by such wild relatives of these plants has the potential to free these wild relatives from what may be an important ecological constraint. The conclusions of the 2004 FIFRA SAP are consistent with the idea that it may not be possible to apply a general exemption rationale to all PVCP-PIPs. The report concluded that "…PVCP-PIPs [have] no inherent capacity to harm the environment." However, "[i]t was recognized that knowledge of hybridization potential was sparse and of very unequal quality but the likelihood of serious economic harm was such that some plants engineered to contain stress tolerant traits should not be released" (Ref. 25). The 2005 SAP's conclusions discussed above also clearly suggest that crops containing a PVCP-PIP that have wild relatives must be carefully considered on a case-by-case basis (Ref. 11). Similarly, the 2000 National Research Council (NRC) report recommended that because of concerns associated with hybridization with weedy relatives, "EPA should not categorically exempt viral coat proteins from regulation under FIFRA. Rather, EPA should adopt an approach, such as the agency's alternative proposal…, that allows the agency to consider the gene transfer risks associated with the introduction of viral coat proteins to plants" (Ref. 10).

*D. Viral Interactions.*

1. *Scientific issues.* In addition to weediness, a key issue associated with PVCP-PIPs is the question of whether they could affect the epidemiology and pathogenicity of plant viruses. Given the potential impact of virus infection, such changes might affect competitiveness of plant populations thereby altering ecosystem dynamics, e.g., through significant changes in species composition of populations, resource utilization, or herbivory.

The genetic material of plant viruses may be composed of either RNA or DNA, although most have RNA genomes (Ref. 56). Although there are significant differences between RNA and DNA viruses, both are obligate parasites that usually move from plant to plant via vector-mediated transmission. Such transmission, in connection with other

**Deleted:** *vi. Registration.* As discussed in Unit II.B, the standard for exemption differs from the standard for registration. The Agency may not be able to conclude that a PVCP-PIP is low risk, but may be able to conclude that when it is used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment. Thus, an applicant may still apply for a registration under section 3 of FIFRA for a PVCP-PIP that does not qualify for the exemption. In addition, EPA recognizes that the exemption criteria may not identify all low risk PVCP-PIPs. A case-by-case review for registration would allow the Agency to evaluate factors not readily incorporated into clear, unambiguous exemption criteria. For example, if criterion (a)(2) is finalized as the more narrow criterion that the Agency is proposing, and no plant with wild or weedy relatives in the United States would meet the criterion, EPA could consider additional factors under a registration review that would affect the potential impacts of acquisition of a PVCP-PIP, e.g., the effect of virus infection on such species, the existence and impact of any natural virus resistance in the population, the overlap of the plant's distribution with crop cultivation areas, and other relevant traits. As part of registration, the Agency could also impose conditions of use as appropriate.¶ 2

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types of virus transmission, commonly leads to mixed viral infections in crops and other plants (Ref. 57). In natural, mixed infections, viral genomes from different strains and/or different species simultaneously infect the same plant and thus have opportunities to interact (e.g., through recombination, heterologous encapsidation, or synergy). In spite of many opportunities for interaction in nature, such events rarely lead to any detectable adverse outcome (Ref. 58). However, such *in planta* interactions have the potential to result in a virus that causes increased agricultural or other environmental damage.

In transgenic plants containing PVCP-PIPs, every virus infection can be considered in one sense to be a mixed infection with respect to the coat protein gene (Ref. 59). The key questions facing EPA are whether interactions between such introduced plant virus sequences and infecting viruses in transgenic plants may increase in frequency or be unlike those expected to occur in nature (Ref. 60). The Agency has written a literature review addressing these questions (Ref. 60) and will briefly describe the issues associated with recombination, heterologous encapsidation, and synergy below. EPA provides a general overview of each of the processes separately, followed by a brief review of relevant field studies that investigated these processes.

i. *Recombination.* Recombination is a natural process that can occur during replication of DNA or RNA whereby new combinations of genes are produced. Plant virus recombination can occur between members of the same virus pathotype in natural infections, contributing to the number of variants that exist within that pathotype. Recombination can also occur when different viruses coinfect the same plant and interact during replication to generate virus progeny that have genetic material from each of the different parental genomes. Although recombination likely occurs regularly in mixed viral infections, recombination only rarely leads to viable viruses and even more rarely to viruses with truly novel behavior and/or characteristics or any detectable adverse outcome. In order to persist in nature, a recombinant virus must be competitive with variants of the parental viruses that have already demonstrated success in all stages of the infective cycle, e.g., transmission, gene expression, replication, and assembly of new virions (Ref. 58). An analysis of cucumber mosaic virus (CMV) isolates in natural populations showed that viable recombinants were very rarely recovered in mixed infections (Ref. 61).

Although selection in the field appears to act against persistence of new, recombinant viruses, recombination is thought to play a significant role in virus evolution, presumably because recombinant viruses are on very rare occasions able to outcompete existing viruses. How a virus with increased pathogenicity or altered epidemiology might conceivably be created through recombination was suggested by a laboratory experiment in which a pseudorecombinant strain was created by experimentally combining regions of the CMV and tomato aspermy virus (TAV) genomes. This artificially manipulated virus was found to cause more severe symptoms than either of the parental genomes, although the recombinant was not a fully-functional virus as it was not able to move beyond the initially infected cells (Ref. 62) and would therefore not be expected to persist in nature. Another laboratory experiment has shown interspecific recombination between CMV and TAV under conditions in which recombinants would not be expected to have any particular fitness advantage (Ref. 63). In

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another example, alteration of the host range of tobacco mosaic virus (TMV) occurred when a chimeric virus expressed the coat protein from alfalfa mosaic virus (AMV) instead of its own (Ref. 64).

Evidence of past recombination having led to the creation of new RNA viruses has been documented in a number of different groups including bromoviruses (Ref. 65), luteoviruses (Ref. 66), nepoviruses (Ref. 67), and cucumoviruses (Ref. 68). Sequence analysis of viruses from the family *Luteoviridae* indicated that this family has evolved via both intra- and interfamilial recombination (Ref. 69). Interspecific recombination between two related potyviruses, soybean mosaic virus (SMV) and bean common mosaic virus (BCMV) apparently led to the creation of watermelon mosaic virus (WMV) with a broader host range than either SMV or BCMV (Ref. 70). Whereas these latter two viruses are generally restricted to *Leguminosae*, WMV has one of the broadest host ranges among the potyviruses being able to infect both monocots and dicots. For RNA viruses, evidence of recombinant viruses arising in recent history have not been reported, suggesting that the significance of recombination in RNA virus evolution is apparent only over a longer timescale.

Recombination has also played a role in the evolution of new DNA viruses including caulimoviruses (Ref. 71) and geminiviruses (Refs. 72 and 73). For DNA viruses, geminiviruses in particular, several instances can also be cited in which relatively recent recombination events appear to have resulted in the creation of new viruses. For example, a recent epidemic of severe cassava mosaic disease in Uganda is thought to be due to the combination and/or sequential occurrence of several phenomena including recombination, pseudorecombination, and/or synergy among cassava geminiviruses (Ref. 72). It also appears that tomato-infecting begomoviruses that have emerged in the last 20 years around the Nile and Mediterranean Basins probably resulted from numerous recombination events (Ref. 74). In addition, a natural recombinant between tomato yellow leaf curl Sardinia virus and tomato yellow leaf curl virus was detected in southern Spain with a novel pathogenic phenotype that might provide it with selective advantage over the parental genotypes (Ref. 75). Finally, analysis of a newly described *Curtovirus* species associated with disease of spinach in southwest Texas suggests that it may be the result of recombination among previously described *Curtovirus* species (Ref. 76).

In addition to virus-virus recombination, recombination has also been found to occur between virus and plant host RNA. Sequence analysis of the 5' terminal sequence of potato leafroll virus (PLRV) suggests that it arose via recombination with host mRNA (Ref. 77). Evidence suggests that such recombination events can affect virus virulence (for review see Ref. 78). Like a plant host genome, transcripts of viral transgenes would be available for recombination with infecting viruses, and portions of the transgene could thus be incorporated into the replicating virus. Several laboratory experiments have investigated the potential for recombination between viral transgenes and infecting viruses of the same species. These experiments show that recombination can occur between viral transgenes and both RNA viruses (Refs. 79, 80, 81, 82 and 83) and DNA viruses (Refs. 84, 85, 86 and 87). However, the relevance to PVCP-PIPs of the latter experiments with DNA viruses is unclear because the transgenic plants used in the experiments actually show no viral resistance; attempts to develop transgenic DNA virus-

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resistant plants in general have had little success (Ref. 57). In addition, to facilitate the detection of recombinants, most of these experiments were conducted under conditions of high selective pressure favoring the recombinant, i.e., only recombinant viruses were viable. The selective pressure under normal field conditions would likely favor the parental viruses rather than a recombinant as parental viruses will be competent in all of the functions needed for propagation and will outnumber the new recombinant.

ii. *Heterologous encapsidation.* Heterologous encapsidation occurs when the coat protein subunits of one virus surround and encapsidate the viral genome of a different virus. The coat protein, possibly in conjunction with other viral factors, is often essential for transmission and responsible for conferring the high degree of vector specificity. Therefore, a heterologously encapsidated viral genome may be transmitted by the vectors of the virus contributing the coat protein rather than the vectors of the virus contributing the viral genome. For many viruses, transmission from plant to plant occurs by insect vectors, and each virus tends to be transmitted by only one type of insect (Ref. 1). To the extent that vectors visit different groups of plants, vectors carrying a heterologously encapsidated viral genome may carry it to a plant the virus does not normally encounter (Ref. 59).

Most evidence of heterologous encapsidation is derived from laboratory or greenhouse studies. Even though there is a high frequency of mixed infections in nature, most mixed infections do not lead to heterologous encapsidation, and those virus interactions that do occur tend to be very specific rather than random interactions between unrelated viruses (Ref. 88). Only among some types of plant viruses is heterologous encapsidation regularly observed. Its frequency depends on the relationship between the viruses involved, being more likely to occur among closely related viruses (Ref. 89). An expansion of aphid vector specificity due to heterologous encapsidation was first observed in plants infected with two different isolates of barley yellow dwarf virus (BYDV; Ref. 90) and was later shown to be a general phenomenon among these viruses in natural populations of several plant species (Ref. 91). Heterologous encapsidation was also shown to occur in potyviruses. An isolate of zucchini yellow mosaic virus (ZYMV) that is normally non-aphid transmissible due to a transmission-deficient coat protein was found to be transmitted by the aphid vector due to heterologous encapsidation when in a mixed infection with another potyvirus, papaya ringspot virus (Ref. 92). Heterologous encapsidation is essential for movement of some viruses. For example, umbraviruses do not encode a coat protein, and therefore transmission between plants occurs through encapsidation by an aphid-transmissible luteovirus coat protein (Ref. 93).

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Heterologous encapsidation is considered a possible environmental concern associated with PVCP-PIPs because of the potential that if a virus is heterologously encapsidated by a PVC-protein, the viral genome might be able to spread to plants the virus ordinarily had no means of reaching and thus could not have infected. Experimental studies have shown that some PVC-proteins in transgenic plants have the ability to encapsidate even unrelated infecting viruses (Refs. 94, 95, 96 and 97). However, heterologous encapsidation involving a viral transgene can only occur if an expressed coat protein possesses the appropriate physical parameters to encapsidate the viral

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genome of infecting viruses. When transgenic plants containing a PVCP-PIP display resistance with very low or no levels of PVC-protein expression (e.g., due to PTGS), the probability of heterologous encapsidation would be very small or non-existent. (For a more detailed discussion of PTGS and suppression of gene silencing, see Unit II.E. above and Unit IV.F. of the companion document also appearing in today's **Federal Register**.)

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Environmental concerns associated with heterologous encapsidation when PVC-protein is expressed appear to be largely mitigated by several factors. One, the heterologously encapsidated viral genome may not be able to replicate in the new host plant and could therefore not actually infect it. In addition, if replication is possible in the new plant, the replicating viral genome encodes for and thus would produce its own coat protein rather than that which heterologously encapsidated it. This virus would not be transmitted by the new vector that brought the heterologously encapsidated genome to the new host plant. The epidemiological consequences of such heterologous encapsidation would thus be limited. Another consideration for some viruses is that effective vector transmission may depend on more than the coat protein (Refs. 98 and 99), requiring regions of the viral genome not included in PVCP-PIPs as defined for this proposal, e.g., coat protein read-through domains or helper factors. Thus, in such cases, the coat protein that could potentially heterologously encapsidate another viral genome would not contain all the parts necessary to lead to a change in vector specificity. In addition, in large monocultures of crop plants, a vector is most likely to move from plant to plant within the field and to transmit even a heterologously encapsidated viral genome to a plant that the virus is already able to infect (Ref. 98). Finally, as with recombination, as long as the PVC-protein expressed in the transgenic plant is from a virus that normally infects the plant in the area where it is planted, the outcome of any heterologous encapsidation that may occur is expected to be the same in transgenic plants as in natural, mixed infections.

In addition to these considerations, EPA evaluated whether a virus that is heterologously encapsidated and carried to a new host plant might be exposed to a vector that feeds on the new host plant and perhaps other plants the virus ordinarily could not access. EPA considered whether this new vector might in some cases be able to transmit the virus even though the virus would now be encapsidated in its own coat protein, thereby expanding the virus' vector range. A new vector could possibly transfer the virus to new host plants, thus expanding the plant host range as well (Ref. 57). EPA considers expansion of host range through heterologous encapsidation to be an extremely unlikely outcome because such an outcome depends on each event in a series of rare events occurring. Should the probability of occurrence of any one event in this series be zero, the adverse event of an expanded host range would not occur. In addition to the events enumerated above, additional events must also occur. First, a virus must be heterologously encapsidated, an event that is possible only for some viral genome-coat protein combinations. Second, a new vector must transmit the encapsidated viral genome. Third, the transmission must be to a new host plant. Fourth, the heterologously encapsidated viral genome must be able to replicate in the new host plant. Fifth, the resulting virus, now encapsidated in its own coat protein, must be exposed to a new vector the virus never encountered before that is nevertheless able to transmit it. Finally, this vector must transmit the virus to a new plant that the virus' prior vectors never visited. For such a series of events to be novel, the viruses, vectors, and plants involved

must have had no previous opportunity to interact, and it is rare for such a condition to be met. For example, it is known that many viruses are transmitted by polyphagous insects, which would have already allowed the viruses to be introduced to many potential plant species even in the absence of heterologous encapsidation (Ref. 57). Moreover, viruses may be transmitted at low frequency by a range of species other than their primary vector or mechanically, e.g., through the practices of modern agriculture (Ref. 98).

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Another scenario EPA considered is one where a high enough frequency of vector transmission to a new host plant due to heterologous encapsidation might mean that secondary spread among new plant hosts might not be required for the phenomenon to affect the population, assuming that the virus is able to decrease the new host plant's growth and/or reproduction. Although this scenario may be more likely to occur than an expansion of host range given that fewer rare events would have to occur, any impact on the affected plant population would be highly localized being confined to plants in or near transgenic crop fields. Such negative impacts are unlikely to be sufficiently detrimental to require FIFRA regulation given their localized nature and the probability that common agricultural practices (e.g., vector control) could be used to manage the problem. Moreover, although isolated instances of transmission may occur, a significant proportion of a plant population is unlikely to be infected in such a scenario. For example, a field experiment (discussed in Unit III.D.1.iv.) showed that heterologous encapsidation led to infection of only 2% of plants compared to 99% of plants infected under similar conditions by a virus that is not heterologously encapsidated (Ref. 100). Most importantly, the heterologously encapsidated virus will still have no way to spread among or beyond the plants of the affected population. In the case where a plant population contains relatively few individuals such that the impact of single plant infections would be magnified, plant infections are even less likely to occur because in addition to the inefficient nature of heterologous encapsidation, the vector would be more likely to feed on the more abundant transgenic crop plants. In some cases a vector may have a strong preference for a specific plant over even closely related plants (Ref. 101).

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Finally, EPA evaluated whether after expansion to a new host, rapid selection of variants best adapted to the new environment might lead to the evolution of a new virus (Ref. 57). However, in addition to requiring several of the rare events discussed above to occur, this phenomenon is unlikely to be entirely novel in any circumstance. All viruses that are occasionally heterologously encapsidated and transmitted to a new plant host have had the opportunity to adapt to new plant environments. The opportunities for rapid viral evolution presented by transgenic plants containing PVCP-PIPs would not be fundamentally different from what occurs in nature under reasonably likely circumstances. Rapid viral evolution after heterologous encapsidation is not dependent on the unique combination of viruses that interact but rather the introduction of a virus to a new plant host, an event that likely occurs in nature at some frequency for most viruses either through heterologous encapsidation or through occasional transmission that occurs mechanically or from secondary vectors (Ref. 98).

iii. *Synergy.* In synergy, another type of viral interaction, the disease severity of two viruses infecting together is greater than expected based on the additive severity of each virus alone. For example, when a plant containing potato virus X (PVX) is

coinfected with any of a number of potyviruses including tobacco vein mottling virus, tobacco etch virus, and pepper mottle virus, the disease symptoms are considerably worsened and PVX accumulates to a greater concentration (Ref. 102). A listing of reported viral synergisms has been compiled (Ref. 103).

In developing this proposal, EPA addressed whether synergy could occur between an infecting virus and a PVCP-PIP, thereby increasing the severity of the infecting virus and whether any consequences for the environment could result from such an increase. For disease severity to worsen, the PVC-protein must be at least one of the factors causing synergy. However, the coat protein is considered much less likely to be responsible for synergism than other parts of the virus (Refs. 104 and 105), and a PVCP-PIP producing other viral proteins would not qualify for this proposed exemption. In addition, any negative effects are expected to manifest primarily in the transgenic crop itself. Furthermore, any negative effects are expected to be self-limiting because any plants containing a PVCP-PIP that is prone to display synergy with viruses common in the areas of planting would be quickly abandoned once such effects were detected, perhaps as early as the field-testing stage of product development. Synergistic interactions can be evaluated in transgenic plants before deployment by experimental inoculation with all of the viruses likely to be encountered in the field (Ref. 98). Developers have a strong incentive to undertake such efforts to ensure the efficacy of their product after deployment.

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iv. *Field experiments.* The experiments referenced in Units III.E.2.i. through iii. above investigated potential viral interactions in transgenic plants containing a PVCP-PIP under laboratory conditions. However, equally important is consideration of the likelihood and potential impact of viral interactions under natural field conditions (Ref. 106). Relatively few field studies have been conducted to address the questions EPA is evaluating for this proposal, but the Agency has carefully considered the available literature in developing this proposed exemption.

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A six-year experiment searched for and failed to find evidence of interactions involving viral transgenes in 25,000 transgenic potato plants transformed with various PLRV coat protein constructs. Plants were exposed to infection by PLRV by direct inoculation, plant-to-plant spread, or natural exposure. In field experiments, plants were also naturally exposed to the complex of viruses that occur in the region. Both the greenhouse and field tests failed to show any change in the type or severity of disease symptoms, and all viruses isolated were previously known to infect the plants and had the expected transmission characteristics (Ref. 107). These results suggest that viral interactions leading to evolution of new viruses and/or more severe viral disease are events too rare to be detected in a field trial of this size and duration.

A two-year experiment with transgenic melon and squash expressing coat protein genes of an aphid-transmissible strain of CMV failed to yield evidence that either recombination or heterologous encapsidation enabled spread of an aphid non-transmissible strain of CMV in the field (Ref. 108). A similar experiment used transgenic squash expressing coat protein genes of an aphid-transmissible strain of watermelon mosaic virus (WMV). Plants were mechanically inoculated with an aphid non-transmissible strain of ZYMV, and subsequent transmissions of the virus (assumed to be

vectored by aphids) were assessed. Infections of ZYMV were not detected in nontransgenic fields, but the virus infected up to 2% of plants in transgenic fields. Several lines of evidence suggested ZYMV infection was mediated by the WMV PVC-protein heterologously encapsidating the ZYMV viral genome. However, the virus spread over short distances, and transmission at a low rate failed to lead to an epidemic of ZYMV in fields of WMV-resistant transgenic squash despite the presence of optimal conditions for transmission (Ref. 100). These results support the contention that even if heterologous encapsidation involving a PVC-protein were to occur, the impact is likely to be negligible because each plant infection by a heterologously encapsidated virus requires a series of rare events to occur. Viral infection by normal routes of transmission can be at least an order of magnitude more efficient and lead to relatively greater impacts (Ref. 100).

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An experiment to assess the biological and genetic diversity of California CMV isolates sampled before and after deployment of transgenic melon containing the CMV coat protein gene documented only one CMV isolate that had significant sequence changes. However, the same change was seen with infection of non-transgenic plants, suggesting that this isolate did not result from recombination between the transgene and an infecting virus (Ref. 109). The only field experiment to directly assess the effect of recombination in a transgenic plant containing a PVCP-PIP found no detectable grapevine fanleaf virus (GFLV) recombinants containing the inserted coat protein sequence over the course of a 4-year study (Ref. 110). Test plants consisted of nontransgenic scions grafted onto transgenic and nontransgenic rootstocks that were exposed over 3 years to GFLV infection at two locations. Analysis of challenging GFLV isolates revealed no difference in the molecular variability among isolates from 190 transgenic and 157 nontransgenic plants, or from plants within (253 individuals) or outside (94 individuals) of the two test sites.

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*2. Proposed exemption criterion*. The information in Units III.E.2.ii. through iv. suggests that heterologous encapsidation very rarely leads to changes in virus epidemiology that could have any large-scale impact and that synergy in plants containing PVCP-PIPs is also unlikely to cause any widespread environmental harm. Consistent with these observations, the 2004 SAP noted that "except perhaps for a very few cases, neither heterologous encapsidation nor synergy should be considered to be of serious concern" (Ref. 60). However, the Agency believes that in all cases, concerns associated with these types of viral interactions are likely to be limited in scope (for reasons discussed in Units III.E.2.ii. through iii.) such that the determination can be made that they pose low risk to human health and the environment. EPA therefore concludes that PVCP-PIPs present low risk with respect to heterologous encapsidation and synergy and that PVCP-PIPs could be exempted without further qualification or requirements to address these endpoints.

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However, EPA is not able to conclude at this time that all PVCP-PIPs are low risk with respect to recombination (although see Unit VII. for a discussion of EPA's request for information that might allow the Agency to reach such a conclusion). The Agency notes that the vast majority of interactions between a viral transgene and an infecting virus are expected to be no different from those that would occur in a natural mixed infection of the respective viruses and would not cause any adverse environmental effects

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beyond what could occur in the absence of the PVCP-PIP. Nevertheless, the information discussed in Unit III.D.1.i. suggests that recombination among viruses may lead to rare instances of adverse changes in virus epidemiology and/or pathogenicity, e.g., a host range expansion. Based on the available information, EPA is not able to rule out that viable, recombinant viruses containing a portion of a PVCP-PIP could arise in transgenic plants and that in a small set of circumstances (discussed in Unit III.D.2.j.) such recombinants could be unlike those that could arise naturally. EPA agrees with the conclusions of the 2004 SAP that "[i]n contrast to heterologous encapsidation and synergy, at least in theory, the impact of recombination could be much greater, since there is now abundant bioinformatic evidence that recombination has indeed, as long suspected, played a key role in the emergence of new viruses over evolutionary time" (Ref. 25). The 2005 SAP concurred with this conclusion by noting that there "are a few scenarios, however, in which recombination may have an incrementally higher probability of creating a virus with new properties… In conclusion, the Panel recommended the need for the Agency to have criteria to assess the level of risk" (Ref. 11).

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The Agency notes that the 2005 SAP concluded that "the likelihood for 'novel' interactions is very low, and the environmental concerns that might result from using PVCP-PIPs in the United States… is lower than that which occurs naturally from mixed virus infections" (Ref. 11). In addition, "it was repeatedly stated that the consequences of any recombination event are minimal. This conclusion was based on the fact that nearly every plant on the planet is harboring multiple virus infections with both closely related and taxonomically distinct viruses, with essentially no new viruses emerging with substantially different properties and causing wide pandemics or undesirable environmental effects" (Ref. 11). In spite of such comments, EPA's proposal contains § 174.27(b) because of the overall context of the Panel's response which articulated several factors (discussed in Unit III.D.2.) that should be considered when evaluating recombination. EPA believes § 174.27(b) is consistent with these comments of the 2005 SAP because the Agency believes these comments apply only when considering the whole set of PVCP-PIPs that are likely to be developed. For the PVCP-PIPs that would only qualify for an exemption without the limitations provided by § 174.27(b), EPA does not believe the Agency can conclude low risk with respect to recombination because the 2004 and 2005 SAPs have identified specific instances where this general conclusion may not hold.

The few field evaluations conducted (discussed in Unit III.D.1.iv.) suggest that adverse environmental effects due to recombination in transgenic plants containing PVCP-PIPs are unlikely to occur at least on a small scale over a short time period. However, large acreages of plants containing a PVCP-PIP grown over many years may provide increased opportunity for rare events to occur that are unlikely to be detected in experimental studies (Ref. 104). In addition, none of the experimental systems described above would be predicted to involve viruses that would otherwise not be expected to interact in a mixed infection found in nature. Given the limited amount of field data available, particularly data relevant to the circumstances EPA has identified as being of highest concern (i.e., those that could lead to novel interactions), EPA is limiting the proposed exemption to those PVCP-PIPs for which novel viral interactions are unlikely

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to occur. When EPA consulted the 2004 SAP about situations in which novel viral interactions might be a concern, the Panel agreed "that recombination is a concern when the two contributing viruses have not previously had a chance to recombine" (Ref. 25).

In addition to considering the potential for novel viral interactions to occur, EPA also considered whether transgenic plants containing PVCP-PIPs might have a changed *frequency* of viral interactions. The frequency could *decrease* because the cellular concentration of viral RNA transcripts expressed from transgenes may be orders of magnitude lower than the concentration of viral RNA commonly found in natural, mixed infections (Ref. 111), reducing the opportunity for recombination. The concentration of infecting viral RNA from the target virus would also be reduced considerably if the PVCP-PIP is efficacious, particularly when the mechanism of resistance relies on PTGS to remove viral RNA transcripts with homology to the transgene (Ref. 112), thereby also reducing the opportunity for recombination. However, the frequency of interactions could also *increase* given that transgene RNA expressed from a constitutive promoter could be available for interactions with infecting viruses in all cells of the plant at all times – unlike RNA from a virus in a natural infection. When a virus invades a cell, it often replicates and then moves to other cells within the plant. The RNA remaining in the initially infected cell becomes encapsidated and may no longer be available for interactions with another invading virus (Ref. 113). When EPA presented this issue to the 2004 SAP, the panel responded that "no increase in heterologous encapsidation should be anticipated in PVCP-PIP plants" and "the Panel believed that in general recombination was more likely to occur in transgenic plants than in non-bioengineered plants." Nevertheless, the Panel agreed "that the important questions are not the relative likelihood for recombination to occur, but rather whether recombinants in transgenic plants are different from those in non-transgenic plants and whether they are viable" (Ref. 25). Thus, EPA's proposal focuses on situations in which novel recombination events could occur due to the presence of a PVCP-PIP.

j. *Proposed categorical exemption criterion in §174.27(b)(1).* In developing the proposed categorical exemption for a subset of PVCP-PIPs in which a developer could self-determine whether the criteria were met, EPA sought to clearly identify those situations that pose low risk with respect to viral interactions.

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A PVCP-PIP would meet the viral interactions criterion under § 174.27(b)(1) if:

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(i) The viral pathotype used to create the PVCP-PIP has naturally infected plants in the United States and naturally infects plants of the same species as those containing the PVCP-PIP, or

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(ii) The genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant.

Recombination between the coat protein gene of the PVCP-PIP and infecting viruses would be expected to be of little concern in certain instances: when such recombination would involve segments of viruses that are judged likely to have had the opportunity to recombine in a natural, mixed infection (and therefore any recombinants produced are unlikely to be novel), and when PTGS results in only small, cleaved pieces

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of RNA being available for recombination. The former situation would be met if the conditions of the criterion in proposed § 174.27(b)(1)(i) are met. The latter situation would be met if the conditions of the criterion in proposed § 174.27(b)(1)(ii) are met. EPA is proposing that no further data or information would be needed to evaluate risks associated with recombination when § 174.27(b)(1) is satisfied under either § 174.27(b)(1)(i) or § 174.27(b)(1)(ii), and therefore no Agency review would be necessary. The developer may make this determination.

If the viral pathotype used to construct the PVCP-PIP was isolated in the United States from the same plant species as was engineered to contain the PVCP-PIP, the PVCP-PIP would meet the proposed criterion in § 174.27(b)(1)(i). It should be noted that this proposed criterion would be used in concert with the proposed protein production criterion in § 174.27(c) discussed below in Unit III.E.2., which ensures that any modifications from the natural isolate encode a protein that is no more than minimally modified from a natural virus coat protein. Thus, any coat protein that satisfies § 174.27(c) would be extremely unlikely to confer significantly different properties on any virus that could potentially acquire the coat protein through recombination with the genetic material of the PVCP-PIP.

The Agency asked the FIFRA SAP during the October 2004 meeting to what extent PVCP-PIPs in plants might present a potential concern should interactions with infecting viruses occur. The Panel expressed concern only "about certain limited situations" and clarified that "in most cases there is little *a priori* reason to believe that recombinants between viruses and transgenes will be more of a problem than recombinants between two viruses infecting the same plant, unless transgenes are derived from severe or exotic isolates. The general recommendation to use mild, endemic isolates as the source of the transgene (e.g. Hammond et al. 1999) should minimize any potential for creation of novel isolates that would not equally easily arise in natural mixed infections" (Refs. 25 and 57). The Agency's proposed § 174.27(b)(1)(i) is consistent with this 2004 SAP recommendation because it excludes exotic virus isolates as the source of the PVCP-PIP transgene. Although proposed § 174.27(b)(1)(i) does not require that the virus isolate be a "mild" form of the virus, it does ensure that when virus isolates capable of causing severe cases of viral disease are used, the PVCP-PIP may only meet § 174.27(b)(1)(i) if the viral pathotype was present in the natural system and therefore should pose no risk of novel interactions.

The 2005 SAP offered a decision flowchart indicating a point at which the Agency should identify the few scenarios where recombination may be of concern: "the question arises as to whether recombination of the sequence could lead to a significant change in the properties of the recombinant over the original properties of the superinfecting virus. Significant changes include increase in pathogenicity, increase of host range or change of vector" (Ref. 11). EPA believes that consideration of whether the conditions of proposed § 174.27(b)(1)(i) are met addresses whether the potential exists for significant changes in the properties of a recombinant virus compared to what might occur in a natural, mixed infection.

In addition to excluding exotic virus isolates, proposed § 174.27(b)(1)(i) also excludes PVCP-PIPs that are inserted into a plant species that is not naturally infected by

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the virus used to create the PVCP-PIP. Most PVCP-PIPs are created from viruses that do naturally infect the plant species into which they are inserted because greater efficacy is achieved when a virus most similar to the target virus is used as the source of the sequence used in the PVCP-PIP. However, virus-resistant transgenic plants have been created where this is not the case (Ref. 114). In these situations, a virus is introduced into a system where it does not naturally occur, and viruses with which it does not otherwise interact may be present in that system. The Agency cannot *a priori* determine that such interactions are safe because there is no experience upon which to base such a finding.

Proposed § 174.27(b)(1)(i) is also consistent with the 2005 SAP's recommendation to consider "whether recombination of the sequence could lead to a significant change in the properties of the recombinant over the original properties of the superinfecting virus" (Ref. 11). When the viral pathotype used to create the PVCP-PIP has naturally infected plants in the United States and naturally infects plants of the same species as those containing the PVCP-PIP, the sequences that could interact would be expected to already have opportunities to interact in nature and thus no novel recombinants should be produced.

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The Agency's proposed § 174.27(b)(1)(ii) is consistent with the 2005 SAP's recommendation to consider whether the PVCP-PIP expresses PVC-protein when evaluating the potential consequences of recombination (Ref. 11). When a PVCP-PIP expresses no PVC-protein because it is designed to mediate resistance through PTGS, recombination would be of little concern because "recombination between a full-length viral RNA and a cleaved small RNA resulting from PTGS would yield a truncated non-functional RNA. Therefore, a PTGS transgene poses negligible potential to yield novel recombinant viruses" (Ref. 11). EPA therefore makes part of its proposal two circumstances when, according to the 2005 SAP, the PVCP-PIP can only mediate resistance through PTGS because it would produce no PVC-protein: when the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant (Ref. 11). See Unit III.D.2.ii. below for a discussion of how other constructs mediating resistance through PTGS could meet § 174.27(b).

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One Panel member noted, "PTGS results in small RNA from the PIP and the infecting virus that could, in certain circumstances, be recombinatorial." However, the Panel concluded "this minimal RNA would not confer a phenotype to the recombinant, would result in just a few nucleotide changes in a potential recombinant, and thus would be irrelevant" (Ref. 11).

EPA proposes to define the term "naturally infect" to mean "to infect by transmission to a plant through direct plant-to-plant contact (e.g., pollen or seed), an inanimate object (e.g., farm machinery), or vector (e.g., arthropod, nematode, or fungus). It does not include infection by transmission that occurs only through intentional human intervention, e.g., manual infection in a laboratory or greenhouse setting." The Agency is proposing this definition specifically to exclude transmission that occurs only through intentional human intervention because such transmission would have little relevance to normal virus infection. EPA recognizes that humans may play an inadvertent role in

infection (e.g., by transmitting the virus on farm machinery). Such unintentional (and often unavoidable) transmission can be an important means of virus transmission, leading to the natural presence of viruses in plants. EPA therefore proposes to include this mode of incidental transmission in the definition of naturally infect.

EPA uses the term "viral pathotype" rather than the more generic term "virus" in response to the October 2004 FIFRA SAP comment that "[n]ot all isolates of a virus infect and cause disease in all plant genotypes and, as a consequence, the unqualified use of the term 'virus' when setting a condition for applicants to the Agency [is] not adequate in this context. It is therefore appropriate in the context of biosafety as well as virus epidemiology to recognize the value of defining specific viral pathotypes or host range variants." The 2005 SAP was asked to comment on the use of this term and responded, "there was not much discussion of this term. The Panel suggested that logic says that local or indigenous virus isolates, or those with significant sequence similarity, will be used to generate PVCP-PIPs. From what we know now, only those viruses with high sequence identity will be useful as sources of the PVCP-PIP transgene." EPA agrees that generally viral pathotypes that meet § 174.27(b)(1) will be those most effective for creating PVCP-PIPs and will therefore be the most commonly used. However, EPA considers the limitations imposed by this term to be necessary because the Agency cannot conclude that viruses not meeting this criterion would be low risk with respect to recombination.

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In this proposed criterion and in § 174.27(c) discussed below, EPA uses the phrase "genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance," rather than the phrase "genetic material necessary for the production," to indicate that regulatory regions, such as promoters, enhancers, or terminators, need not be considered in evaluating whether a PVCP-PIP satisfies these criteria. EPA is not proposing to amend the definitions for "genetic material necessary for the production" or "regulatory region," both found at 40 CFR 174.3, and is not seeking any comment on these definitions.

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ii. *Proposed exemption criterion conditional on Agency determination in § 174.27(b)(2).* The Agency recognizes that many PVCP-PIPs may pose low risk with respect to recombination even though they fail to satisfy § 174.27(b)(1). Therefore, EPA is proposing an approach under which PVCP-PIPs that fail to meet § 174.27(b)(1) could still meet § 174.27(b), subject to an Agency review to determine whether they meet a different set of conditions related to this issue. Under this proposed approach, a PVCP-PIP would meet § 174.27(b) under § 174.27(b)(2) if the Agency determines that viruses that naturally infect the plant containing the PVCP-PIP are unlikely to acquire the coat protein sequence through recombination and produce a viable virus with significantly different properties than either parent virus.

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The conditions in proposed § 174.27(b)(1) address the potential for recombinants to arise unlike those expected in natural mixed infections primarily by ensuring that no novel viral interactions occur. Under proposed § 174.27(b)(2), a PVCP-PIP could qualify for exemption even when novel viral interactions could occur providing steps were taken to ensure that an infecting virus would not acquire a portion of the PVCP-PIP coat

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protein sequence through recombination and produce a viable virus with significantly different properties than either parent virus.

Experimental evidence has suggested a number of ways coat protein genes of certain viruses may be modified in constructing a PVCP-PIP to reduce the possibility they would participate in a recombination event with an infecting virus. For example, removing the 3' untranslated region (UTR) in the coat protein mRNA transcript may be effective at reducing recombination for viruses that carry the initiation promoters of RNA replication in this region (Ref. 115). Evidence suggests that recombination among RNA viruses occurs via template switching by the viral replicase during replication such that a hybrid molecule is formed (Ref. 116). Inclusion of the 3' UTR may enable replication to begin on the mRNA transcript and then switch to the RNA of the invading virus. Removal of this region would necessitate two separate template-switching events to form a successful recombinant and thus reduce its likelihood of occurrence (Ref. 80). Experiments with CCMV demonstrated that deletions in the 3' UTR did indeed reduce the recovery of recombinant viruses (Ref. 117). Since functional resistance is still conferred by constructs containing a CP lacking the 3' UTR, this region may not be necessary. Other techniques that have been suggested include:

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• Reducing the extent of shared sequence similarity between the infecting virus and the transgene to reduce the opportunities for homologous recombination (Ref. 118).

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• Excluding any sequences containing replicase recognition sites that are potential sites of recombination and any sequences known or thought to be recombination hotspots, e.g., promoters for genomic and subgenomic RNA synthesis (Ref. 119).

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• Avoiding potential hairpin structures in the transgene that might function as acceptor structures for the replicase complex (Ref. 120).

It is important to note that any PVC-protein produced must be evaluated under § 174.27(c) in order for the PVCP-PIP to qualify for exemption. Some techniques that may enable a PVCP-PIP to meet § 174.27(b)(2) would preclude the PVCP-PIP from meeting § 174.27(c)(1) and necessitate a review under § 174.27(c)(2). For example, a construct could meet proposed § 174.27(b)(2) if it contained portions of several different coat protein genes in tandem, linked together in such a way that if the sequence were translated it would yield a non-functional coat protein of no use to a virus. A virus that acquired this entire sequence through recombination in exchange for portions of its own genome would likely be nonviable. As another example, a construct might meet proposed § 174.27(b)(2) if it contained a very small portion of a coat protein gene. In such cases, a virus would be unlikely to acquire this sequence through recombination without picking up additional pieces of genetic material from the construct or the plant genome that would likely render the virus nonviable. Or, if a virus did acquire a piece of just the small part of the coat protein sequence contained in the transgenic plant, it would likely not be large enough to significantly change the properties of the parent virus. Any PVC-protein produced from either such construct would fail to meet § 174.27(c)(1) but could be evaluated under and may nevertheless meet § 174.27(c)(2) (see Unit III.E.2. below).

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EPA recognizes the comments of the 2004 SAP that "methods for minimizing recombination are only partially effective. For this reason, the question remains whether novel recombinants would be created in transgenic plants, and simply reducing the frequency of these events is not an answer to the question" (Ref. 60). However, EPA believes that a combination of two or more methods, or even perhaps a single method in some cases, could be employed to reduce the expected frequency of recombination such that the Agency would be able to make a determination that a PVCP-PIP would pose low risk with respect to viral interactions. EPA asked the 2004 SAP "which methods are sufficiently effective such that requiring measurement of recombination rates would be unnecessary. The Panel doubted if the …methods [discussed] are sufficiently effective to warrant the reduction of recombination rates below the level that the actual measurement will be unnecessary" (Ref. 25). However, the Agency would have the opportunity during the case-by-case Agency review under § 174.27(b)(2) to consider the particular viral system and whether literature supports the contention that the recombination reduction techniques are likely to be sufficiently effective in the system in which they are employed. EPA anticipates that the Agency could base this determination on the expected reduction in frequency of recombination as determined from the literature and that actual measurement of recombination rates may be unnecessary. Given that there is no universally applicable method for reducing recombination frequency and this type of case-by-case consideration of the particular virus system in question must be conducted, EPA believes an Agency review is needed to make this determination. With an Agency determination under § 174.27(b)(2), EPA would create a criterion that would encompass a larger set of those PVCP-PIPs that pose low risk with respect to viral interactions than are covered under § 174.27(b)(1).

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Section 174.27(b)(2) is consistent with the advice of the 2005 SAP in that it incorporates the portions of the proposed decision tree that allow consideration of whether there are "features controlling recombination," whether "the protein [is] complete," and whether the plant host contains "genes that reduce recombination" (Ref. 11). Likewise, the review procedures for determining whether a PVCP-PIP met the conditions of § 174.27(b)(2) would also be able to consider "the type of RNA-dependent RNA polymerase (RdRps) encoded by the superinfecting virus and the compartmentalization of its site of replication" as suggested by the 2005 SAP (Ref. 11). Although EPA notes that there was some disagreement among the Panel members about the appropriateness of including such information as part of the flow chart, the Agency believes that this information could be reasonably considered when available and when sufficient knowledge about the plant/virus system exists such that it would offer useful information for evaluating this criterion. Overall, § 174.27(b) thus enables the Agency to consider either under § 174.27(b)(1) or § 174.27(b)(2) all of the factors mentioned in the flowchart by the 2005 SAP.

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3. *Historical approaches still under consideration.* EPA's proposed exemption in 1994 did not contain any criteria related to viral interactions. However, since that time, many additional scientific papers and reviews have been published on this topic. Most affirm the general safety of PVCP-PIPs with respect to viral interactions, but some call into question assumptions of how generically this conclusion holds across all PVCP-PIPs. For example, although the 2000 NRC report stated that "[m]ost virus-derived resistance

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genes are unlikely to present unusual or unmanageable problems that differ from those associated with traditional breeding for virus resistance," the NRC's report also suggested that their conclusions were based on the assumption that certain risk management strategies should or would be implemented, e.g., elimination of specific sequences to limit the potential for recombination (Ref. 10). EPA believes the Agency's 1994 conclusion of low probability of risk still holds for most PVCP-PIPs. However, in order to grant an exemption under FIFRA, EPA must be able to make such a finding for all PVCP-PIPs covered by the exemption and must make its safety determination in the absence of any regulatory oversight under FIFRA that could ensure mitigation measures, such as those discussed in the NRC report, were employed. Therefore, it appears prudent at this time to limit this proposed exemption with a criterion that restricts the potential for novel recombination events, as these have been identified as the rare situation in which viral interactions in plants containing a PVCP-PIP may lead to adverse environmental effects.

EPA presented a set of conditions to the 2004 SAP and asked whether they would significantly reduce either the novelty or frequency of viral interactions in plants containing PVCP-PIPs such that the Agency would not need to regulate the PVCP-PIP (Ref. 25). The first proposed condition was that "the genetic material of the PVCP-PIP is translated and/or transcribed in the same cells, tissues, and developmental stages naturally infected by every virus from which any segment of a coat protein gene used in the PVCP-PIP was derived." EPA considered such a condition because with a PVCP-PIP, plants may express viral genes in cells and/or tissues that the virus does not normally infect. Genetic promoters currently used in most transgenic plants cause constitutive expression of transgenes at developmental stages that might otherwise be unaffected by viral infection and often in tissues that the virus does not normally infect (Ref. 113). For example, luteoviruses are normally expressed only in phloem tissue, but the cauliflower mosaic virus (CaMV) promoter, commonly found in existing PIP constructs, would drive expression of luteoviral coat protein in all plant cells. Some evidence suggests that in natural infections different viruses have different temporal or spatial expression patterns that would limit their interactions (Refs. 63, 121 and 122). However, the 2004 SAP concluded that such a condition would be of limited utility because "[m]ost plant viruses are present in a wide range of cell and tissue types" (Ref. 25).

The second condition proposed to the 2004 SAP was that "the genetic material of the PVCP-PIP contains coat protein genes or segments of coat protein genes from viruses established throughout the regions where the crop is planted in the United States and that naturally infect the crop into which the genes have been inserted." EPA considered the first part of this criterion because plants may be engineered with coat protein genes from an exotic strain of a virus that may be more virulent or have other properties different from endemic isolates. Interactions between a PVCP-PIP based on such virus sequences and infecting viruses could potentially change the epidemiology or pathogenicity of the infecting viruses. The 2004 SAP concurred that "using such an exotic coat protein gene would open possibilities for novel interactions." EPA's current proposed § 174.27(b) thus excludes from exemption PVCP-PIPs based on coat protein genes from exotic viruses unless steps have been taken to reduce the frequency of recombination.

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EPA considered the second part of this 2004 criterion (i.e., the genetic material of the PVCP-PIP contains coat protein genes or segments of coat protein genes from viruses… that naturally infect the crop into which the genes have been inserted) because in heterologous resistance a plant may be resistant to infection by a particular virus in spite of having the coat protein gene of another virus incorporated into its genome. For example, coat protein genes from LMV were used to provide resistance to PVY in tobacco which is not infected by LMV (Ref. 114). In such plants, LMV sequences might have a new opportunity to interact with viruses that infect tobacco. The 2004 Panel concluded that "[w]hat is described here is most often implemented: in designing a PVCP transgene, better efficacy is often observed if it is as similar as possible to the target virus." Nevertheless, EPA believes that EPA's current proposed criterion (b) is appropriate given that PVCP-PIPs may be developed using heterologous resistance. This criterion excludes from exemption PVCP-PIPs used in plants that the virus used to create the PVCP-PIP does not naturally infect unless steps have been taken to reduce the frequency of recombination.

The third condition proposed to the 2004 SAP was that "the PVCP-PIP has been modified by a method scientifically documented to minimize recombination (e.g., deletion of the 3' untranslated region of the coat protein gene). As discussed above, the 2004 SAP expressed reservation about such a criterion, and EPA recognizes that any single method for minimizing recombination may be only partially effective (Ref. 60). However, EPA believes that a combination of two or more methods, or even perhaps a single method in some cases, could be employed such that the expected frequency of recombination would be reduced to a level that would support determination that a PVCP-PIP would pose low risk with respect to viral interactions, but that such a determination could only be made on a case-by-case basis. EPA thus intends that the proposed criterion in § 174.27(b)(2)(ii) would allow the Agency to make this determination after review.

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The fourth condition proposed to the 2004 SAP was that "the PVCP-PIP has been modified by a method scientifically documented to minimize heterologous encapsidation or vector transmission, or there is minimal potential for heterologous encapsidation because no protein from the introduced PVCP-PIP is produced in the transgenic plant or the virus does not participate in heterologous encapsidation in nature." The 2004 SAP concluded that "[t]his method can … be considered seriously if deemed necessary" (Ref. 25). However, the Agency concluded (as discussed above in Unit III.D.1.ii.) that such methods are not necessary because heterologous encapsidation is so rarely likely to be of any significant ecological concern.

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Based on these considerations, EPA presented a set of modified conditions to the 2005 SAP that reflected the advice of the 2004 SAP. Those conditions were the same as those that EPA is proposing today in § 174.27(b) except that § 174.27(b)(2) as submitted to the 2005 SAP included an additional provision: this criterion could be met by meeting the current conditions *or* by meeting the condition that "the properties of the viral pathotype that are determined by the coat protein gene used to create the PVCP-PIP are substantially similar to the properties of a viral pathotype that naturally infects plants in the United States, and the viral pathotype used to create the PVCP-PIP naturally infects

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plants of the same species as that containing the PVCP-PIP." EPA is no longer proposing this condition as a means of meeting § 174.27(b) because the 2005 SAP concluded that it was "unusable and cannot be re-written into a satisfactory form" because of the difficulty of defining "properties" and "substantially similar" in this context (Ref. 11).

*E. Production of Proteins.*

1. *Scientific issues.* In addition to weediness and viral interactions, a third concern associated with PVCP-PIPs relates to the potential production of proteins (called PVC-proteins) from the plant virus coat protein sequences of the PVCP-PIP, i.e., the potential for human or nontarget organism exposure to proteins that have not previously existed in nature and thus should be examined to determine whether they have potentially toxic or allergenic properties. EPA must consider the safety of any potentially expressed proteins that are part of the PIP when proposing criteria to evaluate PVCP-PIPs for possible exemption.

EPA considered human dietary, human occupational, and nontarget exposure risks in evaluating the safety of PVC-proteins for purposes of this proposal as the Agency must do when evaluating whether a pesticide can be exempt from the requirements of FIFRA. See EPA's assessment of human dietary exposure risks and other non-occupational exposure risks published in the companion document in today's **Federal Register** that proposes to establish a tolerance exemption under FFDCA section 408 for residues of the PVC-protein portion of a PVCP-PIP.

Many, if not all, of the considerations used to evaluate the potential for novel occupational or nontarget exposures can be directly extrapolated from the discussion in this companion document describing EPA's base of experience with viruses infecting food plants. That analysis led the Agency to draw three conclusions on which it is relying to support the proposed tolerance exemption for residues of PVC-proteins in food and which can also be used to support this proposed criterion for exemption from FIFRA requirements. First, virus-infected plants have always been a part of the human and domestic animal food supply. Most crops are frequently infected with plant viruses, and food from these crops has been and is being consumed without adverse human or animal health effects. Second, plant viruses are not infectious to humans, including children and infants, or to other mammals. Third, plant virus coat proteins, while widespread in food, have not been associated with toxic or allergenic effects to animals or humans. EPA derived these conclusions from a sufficient experience and information base to support the proposed tolerance exemption and this proposed criterion for exemption from FIFRA requirements.

EPA consulted the 2004 SAP about possible nontarget effects of PVC-proteins and the validity of the Agency's risk assessment being based on the known history of safe exposure to coat proteins of naturally occurring plant viruses. Virus infected plants have always been a part of the natural environment, and organisms that interact with plants have likely been exposed to plant virus coat proteins over long periods of time. The panel confirmed that PVC-proteins within the range of natural variation of the virus would not be anticipated to present risks to nontarget organisms, concluding that, "[l]ethal effects in animal life after feeding on PVCP-PIP plants are highly unlikely because plant viruses

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are not known to have deleterious effects on animal life. Additionally, animals routinely feed on non-engineered virus-infected plants and do not die…. [S]ublethal effects are not expected to be manifested in animal life, again because wildlife and insects regularly feed on non-engineered virus-infected plants with no apparent sublethal damage" (Ref. 60).

The 2005 SAP echoed these general conclusions by pointing out that virus coat proteins "are naturally present in the environment and no adverse effects to humans or non-targets have been reported" (Ref. 11). However, the 2005 SAP also suggested that additional concerns might warrant evaluation, including "indirect ecological effects (such as altered food sources, vegetative cover, or microbial communities)" (Ref. 11). The particular concerns associated with such effects were not articulated. PVC-proteins that meet the conditions of this exemption are not expected to alter nontarget food sources because they would be so similar to plant virus coat proteins that occur naturally. Indirect effects such as changes in vegetative cover might occur if crop plants containing a PVCP-PIP are larger and/or more productive in the absence of virus infection relative to plants that are infected. However, the overall effect on nontarget organisms is still likely to be minor given that crops are often grown in the absence of viral disease even without the use of a PVCP-PIP, and PVCP-PIPs exempted by this proposal would have very limited ability to spread from crop plants to wild or weedy relatives. PVCP-PIPs are not expected to impact microbial communities because natural plant virus coat proteins are not known to have any toxic mode of action. Moreover, plant virus coat proteins already occur naturally in the environment so microbial communities are already exposed to such proteins. Some Panel members also "expressed concern over potential effects on pollinators," but EPA is unaware of any scientific evidence supporting this concern. EPA concurs with other Panel members who believed that "a history of exposure by pollinators to naturally infected plants can be taken as indicating that there are no novel risks" (Ref. 11).

Other concerns raised by the 2005 SAP regarding nontarget and human non-dietary exposure are addressed in the companion document published in today's **Federal Register,** where they are discussed in the context of consideration of the human dietary risks associated with PVC-proteins. The companion document describes in Unit IV.C, for example, the basis for EPA's conclusion that the hazard associated with PVC-proteins that meet § 174.27(c) of this proposed exemption is sufficiently low that they do not rise to the level warranting regulation. These same arguments can be applied to PVC-proteins that meet § 174.27(c) in this proposal, even in the rare cases when nontarget exposure to a PVC-protein might be greater than the exposure to the corresponding natural plant virus coat protein. The companion document also describes in Unit IV.C. rationales that can be used to support EPA's conclusion that nontarget exposure to PVC-proteins in plant tissues that do not normally contain the corresponding plant virus coat protein is unlikely to contribute significantly to risk. Nontarget organisms would be exposed to natural plant virus coat proteins through a variety of routes and there is no evidence that they would be toxic to any nontarget organisms regardless of the route of exposure.

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2. *Proposed exemption criterion.* As with the other proposed criteria discussed in this document, EPA is proposing that § 174.27(c) would have two parts: Section

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174.27(c)(1) under which a developer may self-determine if a PVCP-PIP meets the conditions, and § 174.27(c)(2) under which the Agency must make the determination.

i. *Proposed categorical exemption criterion in § 174.27(c)(1).* In developing the proposed categorical exemption for a subset of PVCP-PIPs in which a developer could self-determine whether the criteria were met, EPA sought to identify clearly those situations that pose low risk with respect to protein production because any PVC-proteins produced would be within the range of natural variation. EPA wants to ensure that a long history of safe human and nontarget exposure has occurred for any PVC-protein produced from a PVCP-PIP that could qualify for this exemption. A PVCP-PIP would meet § 174.27(c)(1) if a product developer self-determines that:

The genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance:

(i) Is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant, or

(ii) Encodes only a single virtually unmodified viral coat protein. Multiple PVC-proteins could each separately meet this criterion. Chimeric PVC-proteins do not qualify.

EPA intends with the phrase “is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant” to include only those PVCP-PIPs with the specified types of constructs that the 2005 SAP indicated provide a high degree of certainty that no PVC-protein would be produced. Although other types of constructs may also usually not produce any PVC-protein, EPA believes it is necessary to incorporate into its proposal a provision for an Agency review of such constructs. In such a review, EPA could evaluate the level of protein production, if any, that could occur under a variety of circumstances and environmental conditions representative of those that the plant may experience (see Unit III.E.2.ii.). EPA includes the word “only” and the phrase “such that no PVC-protein is produced in the plant” in § 174.27(c)(1)(i) to ensure that the proposed exemption encompasses only those PVCP-PIPs that the 2005 SAP indicated “could be safely determined to have no [PVC-protein] expression regardless of plant tissue, developmental stage, environmental conditions, or exposure to virally-encoded suppressors of PTGS” (Ref. 11). The proposed exemption criterion in § 174.27(c)(1)(i) would not be met by a PVCP-PIP when there are multiple-copy insertions in the plant if any of the copies is not in an inverted repeat orientation or lacking an initiation codon for protein synthesis.

The Agency proposes to define the term “unmodified” to mean, “having or coding for an amino acid sequence that is identical to an entire coat protein of a naturally occurring plant virus. The Agency proposes to define the term “virtually unmodified” to mean, “having or coding for an amino acid sequence that is identical to an entire coat protein of a naturally occurring plant virus, except for the addition of one or two amino acids at the N- and/or C-terminus other than cysteine, asparagine, serine, and threonine and/or the deletion of one or two amino acids at the N- and/or C-terminus.” EPA’s rationale for these proposed definitions and alternative proposals for defining “virtually unmodified” are found in the companion document published in today’s **Federal**

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**Register**. The alternative proposals for virtually unmodified will also be considered as alternatives under this FIFRA proposal.

EPA is proposing to exclude more significantly modified PVC-proteins from the proposed categorical exemption by requiring that the genetic material encode "only a single virtually unmodified viral coat protein." For example, PVC-proteins containing internal insertions, deletions, or amino acid substitutions would be excluded, as would be chimeric proteins that are encoded by a sequence constructed from portions of two or more different plant virus coat protein genes. EPA is proposing to exclude such PVC-proteins from the self-determining part of the exemption in response to the advice of the FIFRA SAP in October 2004 that, "[t]here was general agreement that an allergenicity assessment[3] would be appropriate for insertions or deletions, except perhaps for terminal deletions that do not affect overall protein structure." Insufficient information exists at this time to allow EPA to describe *a priori* a criterion that would ensure all PVC-proteins with modifications other than those encompassed by the definition of "virtually unmodified" fall within the base of experience supporting the proposed exemption. At this time, it is not possible to make a categorical risk assessment finding that other types of changes are unlikely to change the characteristics of any protein produced. Thus, EPA proposes no other modifications be allowed in PVC-proteins that would meet § 174.27(c)(1).

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EPA intends that multiple PVC-proteins expressed in the same plant could each separately meet the criterion in § 174.27(c)(1)(ii) but that chimeric PVC-proteins could not meet this criterion. Chimeric proteins would include PVC-proteins composed of the fusion of two (or more) whole or partial capsid proteins, as well as chimeric proteins that contain a PVC-protein fused with another, unrelated protein. The 2005 SAP concluded that such chimeric proteins could possibly have "completely different antigenic and possibly allergenic properties compared to the properties of the individual capsid proteins" (Ref. 11). EPA is therefore unable to conclude that such proteins would be low risk without a case-by-case review of the protein. EPA intends that multiple, distinct PVC-proteins produced, for example, from a single transgene insertion event or from multiple insertion events in the same plant, could qualify for this exemption because the Agency believes that the properties of each individual protein would be the relevant factors to consider. Some members of the 2005 SAP believed that "EPA evaluations should consider effects of multiple constructs of PVCP-PIPs introduced in transgenic plants" (Ref. 11). The rationale for this concern appears based in part on the potential for a synergistic effect from multiple toxins. However, PVC-proteins produced from a PVCP-PIP that could qualify for this exemption would not be expected to have any toxic mode of action that could cause such a phenomenon. The rationale for this concern appears to be also based in part on the potential for multiple PVC-proteins to "alter 'natural' protein production in plants" (Ref. 11). However, EPA concurs with other 2005 SAP members who "believed that this situation was no different than is likely to occur in nature, where a plant might be infected by multiple unrelated viruses" (Ref. 11). (See also Unit IV.E.1. in the companion document published in today's **Federal Register** for the basis for EPA's conclusion that exposure to plants with different levels of proteins

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[3] The concern relating to the need for an allergenicity assessment is relevant to the Agency's determinations concerning occupational exposures.

elicited by pathogen attack, wounding, or stress, i.e., "pathogenesis-related proteins," likely occurs normally.)

EPA believes the phrase "an entire coat protein" in the definition of "virtually unmodified" conveys that segments of PVC-proteins do not meet the criterion in § 174.27(c)(1)(ii). This limitation is based on the advice of the 2005 SAP that "[d]etermining whether PVC-proteins containing terminal deletions, or any other modifications, are within the range of natural variation would require the development of a database of the natural variation and truncated forms of PVC-proteins that occur naturally." As such, EPA could more appropriately take this consideration into account under the criterion in § 174.27(c)(2)(i) which contains provisions for an Agency review (discussed below in Unit III.E.2.ii.). However, EPA is considering several alternative definitions for "virtually unmodified," some of which may allow truncated PVC-proteins to meet the proposed criterion in § 174.27(c)(1)(ii). These alternatives are presented and discussed in Unit IV.E.1. of the companion document published elsewhere in today's **Federal Register**.

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If the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance encodes only a single virtually unmodified viral coat protein, no novel exposures to humans or nontarget organisms are likely to occur because these PVC-proteins are essentially identical to plant viral coat proteins that are widespread in the plant kingdom, as most plants are susceptible to infection by one or more viruses. EPA is relying on this history of safe exposure to support this proposal. The Agency believes that when such a PVCP-PIP is used, the PVCP-PIP would pose low probability of risk with respect to protein production. EPA is proposing that no further data or information would be needed to evaluate this issue when § 174.27(c)(1) is satisfied, and therefore no Agency review would be necessary.

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ii. *Proposed exemption criterion conditional on Agency determination in § 174.27(c)(2).* The Agency acknowledges that many PVCP-PIPs may pose low risk with respect to concerns associated with protein production even though they fail to satisfy § 174.27(c)(1). EPA is proposing to review such PVCP-PIPs under slightly different factors that the Agency believes also ensure that qualifying PVCP-PIPs pose low risk with respect to concerns associated with protein production. Therefore, EPA is proposing that, under § 174.27(c)(2), a PVCP-PIP would also meet § 174.27(c) if:

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The Agency determines after review that the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance:

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(i) Encodes a protein that is minimally modified from a coat protein from a virus that naturally infects plants, or

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(ii) Produces no protein.

EPA developed the criterion in § 174.27(c)(2) because the Agency recognizes that developers may wish to modify PVCP-PIP constructs to achieve certain product development goals such as greater efficacy, and such modifications might result in changes to the protein(s) produced. Most minor modifications to the genetic material would be unlikely to cause changes to the protein that would be significant from a human or nontarget organism perspective. Under § 174.27(c)(2) EPA may consider such

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modifications on a case-by-case basis. Many of the modifications are likely to produce proteins that fall within the range of natural variation of the virus. However, it is not currently possible to define clearly the range of variation of viruses in general or even of any particular virus as discussed in Unit IV.D. of the companion document published in today's **Federal Register**. Therefore, § 174.27(c)(2)(i) requires an Agency review to determine qualification.

PVCP-PIPs are known to confer resistance by two mechanisms. Resistance may be either protein-mediated, in which the level of resistance is correlated with the level of protein expression, or it may be RNA-mediated, in which the level of resistance is not correlated with the level of protein expression. (See discussion in Unit II.E.) In the case of RNA-mediated resistance, little to no PVC-protein may be produced from the PVCP-PIP. In such cases, little to no risk due to protein production would be associated with the PVCP-PIP. However, the Agency believes that the only conditions that can *a priori* indicate there will be no protein production are encompassed by the criterion in § 174.27(c)(1). Any other type of construct that may confer RNA-mediated resistance through PTGS would be reviewed by the Agency under the criterion in § 174.27(c)(2)(ii). A PVCP-PIP would meet § 174.27(c) if EPA determines that no PVC-protein is produced from the PVCP-PIP.

If protein is produced, today's proposed exemption would cover only those PVC-proteins that are not significantly different from naturally occurring plant viral coat proteins, i.e., proteins that are virtually unmodified or minimally modified. For more significantly modified PVC-proteins, the base of experience upon which EPA relies for support of the proposed exemption would not be applicable. Therefore, EPA would not be able to make the determination *a priori* as part of this proposed rule that the PVCP-PIP poses a low probability of risk to humans and the environment and will not generally cause unreasonable adverse effects on the environment even in the absence of regulatory oversight under FIFRA. However, such PVCP-PIPs may still be eligible for registration, and any significantly modified PVC-proteins could be evaluated as part of the registration review (as discussed in Unit II.G.). (For discussion of the concept of "minimally modified" see Unit IV.E.2. of the companion proposed exemption published in today's **Federal Register**.)

3. *Historical approaches.* EPA's current proposed approach is consistent with what EPA has always intended. EPA has never intended that any proposed exemption for PVCP-PIPs would cover those PIPs that produce proteins significantly different from those that occur naturally (November 23, 1994, 59 FR at 60524; July 19, 2001, 66 FR 37865 and 66 FR 37796).

## IV. Proposed Exemption for Certain Inert Ingredients

As noted in Unit II.F. of this preamble, one of the general qualifications for exemption at § 174.21 is that "any inert ingredient that is part of the plant-incorporated protectant is on the list codified at §§ 174.485 through 174.490." EPA is proposing to add several substances to § 174.486, when they are used in a PIP that is listed in 40 CFR part 174 subpart B – Exemptions and are in a plant that satisfies § 174.27(a):

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- *beta*-D-glucuronidase (GUS) from *Escherichia coli* and the genetic material necessary for its production,

- neomycin phosphotransferase II (NPTII) and the genetic material necessary for its production,

- phosphomannose isomerase (PMI) and the genetic material necessary for its production,

- CP4 enolpyruvylshikimate-3-phosphate (CP4 EPSPS) and the genetic material necessary for its production,

- glyphosate oxidoreductase (GOX or GOXv247) and the genetic material necessary for its production, and

- phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production.

Below is a summary of EPA's finding that these inert ingredients present a low risk to human health and the environment; the docket for this proposed rule contains the Agency's full risk assessment in the document "Environmental Risk Assessment of Plant-Incorporated Protectant (PIP) Inert Ingredients." EPA also proposes to add to subpart X the partial tetracycline resistance gene as present under the control of a bacterial promoter in papaya line 55-1.

EPA has conducted an environmental risk assessment of the PIP inert ingredient phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified plant to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Dekalb's DBT 418 and Ciba Seed's Event 176 Bt corn registrations and Syngenta's COT 102 Bt cotton registration. Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 1997, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the low human health risks associated with this protein (40 CFR 180.1151; 62 FR 17717, April 11, 1997). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA has conducted an environmental risk assessment of the PIP inert ingredient CP4 enolpyruvylshikimate-3-phosphate synthase (CP4 EPSPS) and the genetic material necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified crop to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Monsanto's MON 810 Bt Corn registration. Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 1996, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the

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low human health risks associated with this protein (40 CFR 180.1174; 61 FR 40338, August 2, 1996). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA has conducted an environmental risk assessment of the PIP inert ingredient glyphosate oxidoreductase (GOX) and the genetic material necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified crop to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Monsanto's MON 810 Bt Corn registration. Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 1997, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the low human health risks associated with this protein (40 CFR 180.1190; 62 FR 52505, October 8, 1997). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA has conducted an environmental risk assessment of the PIP inert ingredient neomycin phosphotransferase II (NPTII) and the genetic material necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified crop to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Monsanto's NewLeaf Potato and YieldGard Plus Corn registrations and is discussed in more detail in the *Bacillus thuringiensis* Plant-Incorporated Protectant and MON 863 Biopesticide Registration Action Documents (Ref. 123). Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 1994, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the low human health risks associated with this protein (40 CFR 180.1134; 59 FR 49351, September 28, 1994). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA has conducted an environmental risk assessment of the *Escherichia coli*-derived PIP inert ingredient *beta*-D-glucuronidase (GUS) and the genetic material necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified crop to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Monsanto's Bollgard II Bt cotton registration and are discussed in the Bollgard II Biopesticide Registration Action Document (Ref. 124). Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 2001, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the low human health risks associated with this protein (40 CFR 180.1216; 66 FR 42957, August 16, 2001). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA has conducted an environmental risk assessment of the *Escherichia coli*-derived PIP inert ingredient phosphomannose isomerase (PMI) and the genetic material

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necessary for its production. Topics covered in this assessment include mode of action, ecological effects, endangered species considerations, and gene flow from a modified crop to wild or weedy relatives. Data cited in this assessment were submitted to the Agency in support of Syngenta's MIR604 Bt corn registration. Ecological data and published information on the biology of this protein indicate that this PIP inert ingredient is not known to be toxic and/or pathogenic to plant or animal species. In 2004, the Agency granted a tolerance exemption for this PIP inert ingredient in all plants due to the low human health risks associated with this protein (40 CFR 180.1252; 69 FR 26770, May 14, 2004). Based on all of its assessments, EPA has determined that this inert ingredient will pose low ecological and occupational risk.

EPA believes the partial tetracycline resistance gene as present in papaya line 55-1 presents low risk to human health and the environment and could also be added to 40 CFR part 174 subpart X. No protein is expected to be produced from the gene because it is under the control of a prokaryotic promoter and is only a partial gene that is not expected to function in plants (Ref. 125). Therefore, no ecological or human health effects would be associated with this inert ingredient as found in papaya line 55-1 because it consists of only DNA. Transfer of an antibiotic resistance marker gene from plants to microorganisms in the gut or in the environment may theoretically be possible, but it is extremely unlikely (Refs. 126 and 127). In addition, because only a portion of the tetracycline resistance gene is present in papaya line 55-1, if any horizontal gene transfer of this genetic material were to occur, it would be unlikely to confer antibiotic resistance to any organism that acquired it (Ref. 125).

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EPA asked the 2005 SAP to comment on the Agency's environmental risk assessment for the first six of these selectable markers. The Panel concluded that the "antibiotic resistance marker (NPTII) and other markers (GUS and PMI) should be exempt provided they were in the plant species determined to be of low risk using criteria" the SAP proposed as discussed in Unit III.C.2.i. (Ref. 11) and EPA relied on, as appropriate, in developing the list comprising §174.27(a)(1). In addition, the Panel concluded that the "herbicide markers (CP4 EPSPS, GOX/GOXv247 and PAT) should not be exempted, but rather should be considered on a case-by-case basis taking into consideration the potential that the crop plant has to become feral" (Ref. 11). EPA notes, however, that the only crop plants that will be included on the list comprising §174.27(a)(1) are those whose potential to become feral has been considered. Thus, EPA's inclusion of these six selectable markers in 40 CFR part 174 subpart X – List of Approved Inert Ingredients when they are used in PIPs as inert ingredients in a plant that satisfies § 174.27(a) is consistent with the 2005 SAP's recommendations regarding these inert ingredients.

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EPA is also considering an alternative under which NPTII, GUS, and PMI would be exempt from FIFRA when used as inert ingredients with any exempt PIP, regardless of the plant in which they are expressed. Although the SAP recommended that they only be exempt provided they were used in a plant species determined to be of low risk based on the considerations encompassed in §174.27(a), the Panel did not provide a rationale as to why the markers would not be considered low risk in other plants as well. Given that these markers are widespread in the environment and would be expected to confer no

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particular selective advantage on any plant in the environment that might express them, the Agency knows of no rationale why this limitation would be necessary. The Agency believes that its risk assessment would support such an exemption for these inert ingredients.

EPA is also proposing a technical correction to §174.480 to make the language consistent with the general requirements for exemption, which recognize that for some PIPs no FFDCA tolerance may be required. In such cases, it is not necessary that the inert ingredients have been exempted from FFDCA section 408 requirements.

## V. Economic Analysis

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Virus infection is a serious problem in agricultural production. Virtually every plant species is susceptible to infection by at least one of more than 500 known plant viruses (Ref. 6). Particular crop or weed hosts are nearly always infected by certain plant viruses under natural conditions (Ref. 103). Plant viruses create economic losses for a vast variety of crops by reducing yields and negatively affecting the quality of the crop, damaging fruits, leaves, seeds, flowers, stems, and/or roots (Refs. 103 and 128). Symptom development and vector transmission rates are affected by the environment and so can vary across locations or seasons (Ref. 103).

Virus diseases have often resulted in devastating agricultural losses, at times destroying entire plantings of crops in certain locations (Ref. 103). For example, more than 100 million citrus trees had been destroyed by citrus tristeza virus (CTV) by 1991 in citrus growing regions around the world, including California (Ref. 129). CTV is one of the most economically important viruses because of its widespread distribution, the severity of damage caused by infection, and the long life span of individual trees (Ref. 130).

Growers may need to use several control methods during a crop season in an attempt to prevent viral infection and dissemination, primarily by planting virus-free material for mechanically transmitted viruses. For vector-transmitted viruses, control measures have often focused on chemical insecticides, fungicides, and nematicides to reduce the population of vectors that transmit viruses from plant to plant. However, control of vectors is not always feasible or effective as a way to control virus transmission (Ref. 103). In another common control strategy, crops are grown in rotation with crops that the virus does not infect to reduce the virus load in the field. This method has serious limitations as well. In some cases, the development of resistant cultivars can be the only viable means of virus control. Plants developed through conventional breeding techniques offer some degree of virus resistance. However, breeding for resistance has not been successful for the majority of field crops that are severely affected by viruses (Ref. 128). In some agricultural regions, some crop species cannot be grown effectively because of the persistent presence of infected plant populations and/or potential virus vectors (Ref. 103). Contrary to traditional control measures, transgenic virus-resistant crops offer an effective means of virus protection.

This proposed rule would benefit the public by ensuring protection of human health and the environment while also reducing the cost of and time needed for regulatory

review of transgenic virus-resistant crops. This proposal would also help to appropriately allocate Federal resources for risk evaluation by focusing Agency attention on those PVCP-PIPs that warrant review. This proposed rule would also benefit the industry by removing regulatory uncertainty for this class of products.

This economic analysis (EA) prepared for this proposed rule estimates the projected compliance cost for the industry under the baseline of full registration for all PVCP-PIPs and compares that to the compliance cost for the potentially affected industry under the proposed rule in order to estimate the expected savings from the regulation relief. The steps used to obtain a cost estimate for the proposed rule are summarized below.

Since the nature and timing of future development of PVCP-PIPs are unknown, the EA begins by identifying nine case studies that represent the broadest range of PVCP-PIPs that the Agency anticipates could be developed in the future. After considering the characteristics of the products that have already been marketed, characteristics of the crop plants that have been the subject of field trials for PVCP-PIPs, and knowledge of the field of genetically engineered virus-resistant crops, EPA estimated the percentage of products projected to be characterized by each case study, i.e., the "prevalence" of the case study. The stated prevalence represents the best estimate of the expectation of a PVCP-PIP product like the one in a specific case study being developed in the future.

For each case study, a set of data would be required of a developer in order to register the PVCP-PIP. The cost and burden of potential data requirements for each case study under the baseline are compared with the potential data requirement costs and burden under the proposed option. Using the prevalence for each case study, EPA estimated the probability of developing a PVCP-PIP product like that examined in any of the case studies in any year, given that the Agency anticipates 1.5–2.5 PVCP-PIPs being developed each year over a 10-year period. These probabilities determine the frequency and timing of development and registration of PVCP-PIPs in a model EPA designed to compute compliance cost savings.

To estimate compliance cost savings in any year, the number of PVCP-PIPs like the one developed in a given case study was multiplied by the difference between cost and burden under the proposed rule and baseline. Since the model made use of probabilities, the average of 5,000 simulations was computed for each year to represent the annual compliance cost savings for the proposed rule. Using this procedure, the estimated annual impact, based on average cost estimates per data requirement, is expected to result in a regulatory compliance cost reduction approximately within the range of $340,000 and $360,000 a year. Over a 10-year period, the annual average regulatory compliance cost reduction is expected to be approximately $350,000.

The potential exemptions under the proposed rule, as compared to the baseline under which no PVCP-PIPs are exempted, would reduce regulatory costs for the potentially affected industry and the EPA, remove regulatory uncertainty for industry, and provide important information to the public regarding the safety of exempted PVCP-PIPs. Entities that may benefit from the proposed rule and alternative options are the public, companies that develop and market PVCP-PIPs (applicants and/or registrants),

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farmers, and the environment. However, potential future benefits to these entities are difficult to quantify due to data limitations and uncertain market conditions. In addition, considerable difficulty exists in quantitatively evaluating non-market benefits, such as reduced environmental and human health risks, consistency of regulation, reduced regulatory uncertainty, and improvements in public perception of biotechnology products.

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## VI. Preliminary Statutory Finding

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*A. What Risk Assessment Methodology did EPA use for this Proposed Rule?*

Generally, when EPA assesses the risks caused by the use of a pesticide, it considers both the potential hazard that the pesticide poses to the environment and the potential for exposure to the pesticide due to its use. For most pesticides (e.g., chemical pesticides), EPA relies on data generated by laboratory testing using representative animal models to estimate hazard endpoints. To develop exposure estimates the Agency evaluates other information including product characterization data, proposed use patterns, and information generated from mathematical models. Exposure and hazard estimates are combined to quantify the potential risk associated with the pesticide's use. The data requirements describing the types of information to be generated and other guidance for assessing risk are detailed in 40 CFR part 158.

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The questions posed as part of the risk assessment in evaluating most pesticides (e.g., biological or chemical pesticides) can also be posed for the PVCP-PIPs that are exempted in this proposed action, and 40 CFR part 158 can be used as guidance. EPA adopted an approach for evaluating the potential risks of PVCP-PIPs that is consistent with the unique characteristics of pesticides produced and used in a living plant and the scientific knowledge and experience accumulated on these substances.

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To address the hazard endpoints described in 40 CFR part 158 for the PVCP-PIPs that qualify for this proposed exemption, EPA relied on a very large body of information in the public literature that was developed through many decades of testing and observation. EPA thus did not need to rely on animal model testing for assessing risk as it would for most other pesticides (e.g., chemical pesticides) where specific hazard data are lacking. In addition, PIPs are produced within the living plant, and the pesticidal substance is used *in situ* in the plant. Exposure to PVCP-PIPs is therefore limited relative to exposure to chemical pesticides that are applied broadly in the environment, e.g., through aerial application.

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1. *Large body of knowledge and experience exists.* Typically, in assessing a pesticide for environmental risk, EPA considers data fulfilling the information requirements posed in 40 CFR part 158 to evaluate the potential effect of the pesticide on birds, mammals, freshwater fish and invertebrates, estuarine and marine animals, and nontarget plants and insects (e.g., predators, parasites, and pollinators). For most pesticides, this information must be generated using animal models. To address these same questions for the PVCP-PIPs that are the subject of this proposed exemption, EPA was able to rely on a long history of hundreds, if not thousands of years of natural exposure to plant virus coat proteins by nontarget organisms. EPA relies on these

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experiences and the scientific literature generated by a century of food safety studies (Refs. 131 and 132) to assess the PVCP-PIPs that are the subject of these exemptions.

EPA also took into account the large and varied information base available in the public scientific literature from a number of disciplines including plant genetics, plant physiology, plant virology, weed science, molecular biology, biochemistry, ecology, and plant breeding. For example, the Agency used experimental data derived from the science of plant pathology to characterize the pest resistance mechanisms in plants (Ref. 56) and relied on the scientific knowledge base of plant virology and virus ecology to evaluate how plant viruses interact with each other and with the plant during infection (Ref. 60).

2. *PVCP-PIPs are produced within the living plant, and the pesticidal substance is used in situ in the plant, affecting the exposure paradigm*. EPA used information from the fields of plant pathology, biochemistry, microbial ecology, and ecology in considering all aspects of risk, including exposure. PVCP-PIPs are produced within the living plant itself, and the pesticidal substance is used *in situ* in the plant to protect against pests, in contrast to most other pesticides, which must be applied to or near the plant. Because a PVCP-PIP is produced and used within the plant, physiological constraints limit the amount of pesticidal substance produced by the plant. Regardless of the tissues containing the PVCP-PIP or the level at which PVC-protein is expressed, the PVCP-PIP, including any PVC-protein, is contained within the plant parts. Therefore, the routes by which other organisms may be exposed to the PVCP-PIP may be more limited, e.g., dietary exposure is likely to be the predominant route of exposure, and physical contact with the plant or plant parts will generally be necessary for exposure to occur.

The PVCP-PIPs exempted by this proposed rule are biotic and are subject to the processes of biodegradation and decay that all such materials undergo (Ref. 133). Biotic materials are broken down to constituent parts through the enzymatic processes of living organisms, and these constituent parts are used as building blocks during growth of other biotic substances. In addition, PVCP-PIPs are biodegradable to their constituent elements through catabolism by living organisms. Because of their biodegradable nature, PVCP-PIPs do not bioaccumulate (i.e., build up in tissues because the body is unable to either break the substance down or eliminate it) or biomagnify (i.e., progressively build up in successive trophic levels because it bioaccumulates in the bodies of organisms lower in the food chain). Because of these characteristics, the potential for new exposures to occur beyond direct physical exposures to the plant or plant parts is limited.

A question directly affecting the exposure component of the risk assessment that has no equivalent in the assessment of more traditional pesticides (e.g., chemical pesticides) must be posed for PIPs. Because PIPs are produced and used in the living plant, the possibility that the ability to produce a PIP may be transferred by outcrossing and hybridization from the crop plant to a wild or weedy relative was considered. A large volume of information is available in the public literature to assess the risks of gene flow generally (Refs. 19 and 134) and for PVCP-PIPs in particular (Refs. 12, 32, 36, 135, 136, 137, 138, 139 and 140).

*B. Exemption Determination for PVCP-PIPs, Including Certain Inert Ingredients*.

EPA preliminarily concludes that PVCP-PIPs that meet the criteria specified in this proposed action warrant exemption under FIFRA section 25(b)(2). The use of PVCP-PIPs that meet the criteria in 40 CFR 174.21, including the criteria proposed in this **Federal Register** to be inserted at 40 CFR 174.27 poses a low probability of risk to the environment and is not likely to cause unreasonable adverse effects in the absence of regulatory oversight. EPA bases this preliminary conclusion upon an evaluation of the potential risks that use of PVCP-PIPs qualifying for this exemption would reasonably pose to man and the environment, and upon an evaluation of whether their use causes unreasonable adverse effects. EPA preliminarily concludes that PVCP-PIPs qualifying for this exemption pose a low probability of risk to the environment as demonstrated by information from the fields of plant genetics, plant physiology, plant virology, weed science, molecular biology, biochemistry, ecology, and plant breeding; from many years of experience growing and consuming plants that contain coat proteins from plant viruses; and from Agency knowledge about horticultural and agricultural practices. EPA also believes that use of these plant-incorporated protectants in food is safe under the FFDCA section 408 standard as explained in the preamble to this document and the companion document published elsewhere in this issue of the **Federal Register** exempting residues of the PVC-protein portion of a PVCP-PIP.

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EPA believes that PVCP-PIPs that meet the criteria in 40 CFR 174.21, including the criteria proposed in this **Federal Register** to be added at 40 CFR § 174.27, are also not likely to cause unreasonable adverse effects, even in the absence of regulatory oversight. As a result, EPA concludes that PVCP-PIPs qualifying for this exemption do not cause any unreasonable adverse effects with respect to human dietary risk. Taking into account the economic, social, and environmental costs and benefits of the use of such products, as discussed in the preamble and associated Economic Analysis (found in the docket for this rulemaking), EPA believes that the low levels of risks that such products present do not justify the cost of regulating such products. Note that products that qualify for this exemption would remain subject to the requirement for submission of information regarding adverse effects under 40 CFR 174.71. Even though EPA believes the probability is very low that risks would arise with the PVCP-PIPs qualifying for this exemption, the adverse effects reporting requirement will alert the Agency should any such rare circumstances occur. EPA could then address such instances, as appropriate, under FIFRA.

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## VII. Request for Comment

EPA requests comment on whether the Agency has appropriately identified in this proposed exemption those PVCP-PIPs that are of a nature not requiring regulation under FIFRA. In particular, the Agency requests comment on the following specific issues:

1. EPA requests comment on whether additional plants could be appropriately included in the list of plants comprising proposed § 174.27(a)(1) because they would present low risk with respect to concerns associated with weediness of the plant itself and any wild or weedy relatives of the plant if it were to contain any PVCP-PIP. For example, the 2004 SAP identified the following plants that are not included in proposed § 174.27(a)(1): almond (*Prunus communis*), apricot (*Prunus armeniaca*), cape daisy (*Osteospermum* spp.), chrysanthemum (*Dendranthema* spp.), celery (*Apium graveolens*),

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eggplant (*Solanum melongena*), geranium (*Pelargonium* spp.), hyacinth (*Hyacinthus* spp.), guava (*Psidium guajava*), kiwi (*Actinidia* spp.), nectarine and peach (*Prunus persica*), okra (*Abelmoschus esculentus*), olive (*Olea europaea*), parsley (*Petroselinum crispum*), petunia (*Petunia* spp.), pistachio (*Pistacia vera*), plum (*Prunus domestica*), spinach (*Spinacia oleracea*), taro (*Colocasia esculenta*), tomato (*Solanum lycopersicum*), watermelon (*Citrullus lanatus*), and wishbone flower (*Torenia* spp.).

EPA would be particularly interested in information about these plants or others that addresses the questions in Unit III.C.2.i. that EPA posed to crop experts as part of its evaluation as to whether specific species should be included on the list. In some cases, EPA has already consulted with one or more experts for these plants, but the Agency does not believe it has the information necessary to draw a conclusion for these plants. Given the reliance on expert opinion to make these determinations, EPA would like to have responses from at least three experts for any given crop before including it on the list at § 174.27(a)(1). In other cases, EPA completed at least three consultations, but the Agency received information from at least one expert suggesting that the plant may not meet the low risk standard for inclusion in the § 174.27(a)(1) list, e.g., because of questions about the formation of viable hybrids in nature with wild or weedy relatives or questions about the propensity of the crop to naturalize. EPA describes its analyses in the following paragraphs and requests assistance from the public on the issues raised.

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EPA is inclined to include almond (*Prunus communis*) on the list in § 174.27(a)(1) on the basis of information received from expert consultations. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to introgress into a population of a wild or weedy relative or a naturalized population of the species and what effect such introgression might have. Specifically, the experts indicated that natural hybrids may be able to form with some other stone fruit trees (Ref. 42). However, if such trees are likely to be found in commercial cultivation, natural hybrids would not necessarily be expected in areas outside of managed orchards. Regarding whether almond is a weedy species, both experts mentioned that almond forms feral populations. However, they have not usually required weed management activity because "the trees are infrequent and tend to be seen as beneficial" (Ref. 42). One expert said, "Almond is not highly susceptible to viruses affecting other Prunus tree crop species. Thus virus resistance is not a major determinate of feral almond fitness in current environments…. Thus, it is likely that transgenic resistance would not greatly benefit either commercial or feral almonds" (Ref. 42).

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EPA is inclined to include amaryllis (*Hippeastrum* spp.) on the list in § 174.27(a)(1) on the basis of information received from consultations with amaryllis experts that EPA conducted upon recommendation from other experts in flower breeding. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the weedy characteristics of amaryllis and the potential for gene exchange between feral and cultivated populations. Two experts indicated that there are no wild or weedy relatives in the United States with which amaryllis can form viable hybrids in nature, although one expert said, "*Hippeastrum puniceum* (Lam.) Kuntze is naturalized in Puerto Rico, the Virgin Islands, Louisiana and Hawaii. *Hippeastrum*

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*puniceum* is a diploid species that is occasionally used in breeding programs. In controlled crosses, it will breed with other diploid species, and is probably represented in modern *Hippeastrum* cultivars. However, most modern *Hippeastrum* cultivars available in the florist and greenhouse trade are complex, tetraploid hybrids that are difficult to backcross to *H. puniceum*" (Ref. 42). One expert believed that no species in the genus are known to become feral or easily spread into non-crop areas. However, the others noted that this occasionally occurs without requiring weed management activity. One said, "Hippeastrum puniceum may have been introduced into Puerto Rico, possibly during pre-Colombian times, and it has since sparingly naturalized…. Spread is slow and minimal and has not required management activity" (Ref. 42). Another said, "Plants generally naturalize in disturbed areas along roadsides and irrigation ditches. The species is self-incompatible, but can form seed in naturalized settings. The plants also reproduce asexually via off-sets. Long distance dispersal appears minimal. *Hippeastrum puniceum* is considered a low-risk introduced plant in Hawaii and appears that it does not require active weed-management" (Ref. 42). All three experts agreed that it was unlikely acquisition of virus resistance would cause amaryllis to become feral or easily spread into non-crop areas in the United States. For example, one expert said, "*Hippeastrum* has been grown commercial outdoors since the early 1900's in semi-tropical areas of the US (*Hippeastrum* is not winter-hardy). There has not been a single record of any plants escaping and becoming feral. There is no reason to believe that acquiring transgenic resistance to one or more viruses would increase the ability of plants to become feral or easily spread into non-crop areas" (Ref. 42).

EPA is inclined to include apricot (*Prunus armeniaca*) on the list in § 174.27(a)(1) on the basis of information received from expert consultations. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to introgress into a population of a wild or weedy relative or a naturalized population of the species. Specifically, two experts indicated that apricot may be able to cross with plum species because "[i]f planted in close proximity apricot can be crossed by bees to Japanese plums. That suggests the same could happen with native US plum species, of which there are many in the eastern US" (Ref. 42). However, both experts suggested that the frequency of hybrid production would be extremely low. Two experts indicated that apricot is not known to become feral or easily spread into non-crop areas, while the third expert said that he has "seen rare plants in [Michigan] that are feral or left-over homeowner trees. They did not appear to spread as the big seeds mostly drop under the trees and seem not very competitive compared to the weeds" (Ref. 42). All of the experts agreed that acquisition of virus resistance would be unlikely to change apricot's propensity to become feral. According to one expert, "It is not likely that this would occur because climatic conditions and the occurrence of fungal and bacterial diseases are more limiting than the viruses" (Ref. 42).

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EPA believes that more information about cape daisy (*Osteospermum* spp.) is needed to address issues raised by expert consultation. EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to enhance the potential of species in this genus to naturalize. One expert indicated, "*Osteospermum fruticosum* is a low-risk naturalized plant in Hawaii, and is

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also found, along with *O. ecklonis,* in California. Other *Osteospermum* species have naturalized in Australia and New Zealand. The genus is endemic to the Cape Floristic Region of southern Africa which has a Mediterranean climate. Thus, there is potential for more species of *Osteospermum* to naturalize in California which, like Australia and New Zealand, has a Mediterranean climate…. Transgenic or not, *Osteosperum* [sic] has potential to further naturalize in Mediterranean climates and needs further monitoring for invasive potential in these areas" (Ref. 42). However, the other two experts indicated that it was unlikely that virus resistance would cause cape daisy to become feral or easily spread into non-crop areas. One said, "Other factors are much more likely to limit its invasive potential, such as available moisture, presence of competing vegetation, and predation by insects and vertebrates. Viruses do not appear to be limiting its spread" (Ref. 42). The other expert said, "Viral resistance could conceivably increase fecundity and spread, but there is no data to confirm or refute the possibility" (Ref. 42).

EPA is inclined to include chrysanthemum (*Dendranthema* spp.) on the list in § 174.27(a)(1) on the basis of information received from consultations with two chrysanthemum experts. These experts indicated that there are no wild or weedy relatives in the United States with which commercial chrysanthemum can form viable hybrids in nature. One expert believed that no species in the genus are known to become feral or easily spread into non-crop areas, while the other noted that this has occurred rarely in California, Ohio, Pennsylvania, and Massachusetts. Nevertheless, these populations have not required weed management activity because they "have remained small consisting of only a few plants" (Ref. 42). Both experts believed it unlikely that acquired virus resistance could lead to commercial chrysanthemum becoming feral or easily spreading into non-crop areas. One expert said, "Plants in the genus *Dendranthema* are generally not easily propagated by seed, and are vegatatively [sic] propagated by cuttings or division. They do not compete well with other plants and do not persist in untended garden situations, and would certainly not do so in non-crop areas" (Ref. 42).

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EPA has received one response from an eggplant expert suggesting that eggplant (*Solanum melongena*) meets the requirements for inclusion on the list in § 174.27(a)(1). This consultation indicates that eggplant meets the three conditions outlined above by the SAP: it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make eggplant weedy or invasive. The expert said, "Similar to other species where wild relatives have been utilized to enhance the cultivated form of the crop, genes for improved fitness are derived from the wild relative. Neither the disease resistant wild relative nor the improved cultivars have shown a propensity to become feral" (Ref. 42). EPA is seeking public comment on this determination because the Agency desires a more robust response base.

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EPA believes that more information about geranium (*Pelargonium* spp.) is needed to address issues raised by expert consultation. EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to spread to a wild or weedy population in the United States or enhance the potential of species in this genus to naturalize. Regarding the potential for spread to a

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wild or weedy population, two experts indicated that species within this genus do not form viable hybrids in nature with wild or weedy relatives in the United States, but a third expert said, "In the wild, *P. cucullatum* will hybridize with *P. betulinum* (L.) L'Her. and *P. patulum* Jacq. *Pelargonium grandiflorum* forms natural hybrids with *P. sublignosum* Knuth. The extent to which these hybridizations and other hybridizations occur is not well known" (Ref. 42). Regarding the weedy tendencies of this genus, one expert indicated that "nine species are reported as naturalized or persistent in California… but most occupy disturbed sites near cultivated or urbanized areas" (Ref. 42). Another expert said, "It seems possible that in Mediterranean climates Pelargonium could become a weed problem" (Ref. 42). Two other experts thought that acquisition of virus resistance would not affect the weedy tendencies of this genus. One said, "*Pelargonium* species are notoriously poor seed producers and are all also native to Africa, particularly South Africa. They have specialized ecological niches that would not easily be available anywhere in the U.S. or its territories. California is the most likely place where this could happen, and no incidence of an adventive *Pelargonium* has ever been reported. Viral resistance would not mitigate these factors that prevent adventive establishment" (Ref. 42).

EPA is inclined to include hyacinth (*Hyacinthus* spp.) on the list in § 174.27(a)(1) on the basis of information received from consultations with hyacinth experts. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for hyacinth to naturalize. Three experts consulted indicated that this genus does not form viable hybrids in nature with wild or weedy relatives in the United States. Two experts indicated that there are no naturalized species of *Hyacinthus* in the United States, although a third said, "*Hyacinthus orientalis* has been reported as naturalized in the Blackland Prairies of Texas," but details were not available (Ref. 42). All three experts agreed that acquired virus resistance is unlikely to make hyacinth become feral or spread into non-crop areas.

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On the basis of expert consultation, EPA has concluded that guava (*Psidium guajava*) does not meet the low risk standard needed for inclusion on the § 174.27(a)(1) list. Two experts indicated that more research is needed to establish the potential for outcrossing with wild or weedy relatives. All three experts reported that guava is known to become feral or easily spread into non-crop areas in the United States. One expert stated, "Guava is a vigorous, common, weed in both warm to cool climates. It would likely give this plant additional competitive advantage with transgenic resistance to viruses" (Ref. 42). However, another expert believed that "[g]uava is easily spread without having transgenic resistance. It does not appear that containing resistance to one or more virus [sic] would enhance its ability to become feral" (Ref. 42). EPA requests commenters who believe guava would be appropriate to include on the list in § 174.27(a)(1) specifically to address whether there are wild or weedy relatives with which guava could form viable hybrids in nature in the United States (including Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa) and to address the concern that guava is a weedy species and acquisition of virus resistance could exacerbate these tendencies. Please provide literature citations or other evidence to support any claims contrary to EPA's expert consultations.

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EPA believes that more information about lily (*Lilium* spp.) is needed to address issues raised by expert consultation conducted after recommendation from other flower experts. EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for lily to become feral or spread into non-crop areas and the impact that acquired virus resistance might have on this potential. The experts agreed that in the United States the likelihood of a species in the genus *Lilium* forming viable hybrids in nature with a wild or weedy relative was very small given that lilies do not cross readily. "This is especially true for the hybrids that are adapted or selected for the intensive greenhouse or irrigated gardens' environment. These lilies do not form successful colonies outside these specific environments. The chance that genes will be transferred from gardens to wild populations is negligible" (Ref. 42). However, regarding the weedy tendencies of this genus, one expert said "Several species of Asian or European origin are sporadically naturalized following escape from cultivation, but none strays far or is widespread or common enough to be considered a pest.… *Lilium longiflorum* (Easter lily; Japan) has been recorded from Utah and Florida" (Ref. 42). Another expert said, "*Lilium* [*formosanum*] (Taiwan lily) has been known to invade natural habitats in Northern and Eastern Australia…. Caution would be advised in introducing L. [*formosanum*] into… the US" (Ref. 42). Two experts believed it unlikely that acquired virus resistance would affect the likelihood of lilies becoming feral, although a third said, "Virus resistance might increase the speed and degree with which these exotic species might naturalize" (Ref. 42).

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EPA is inclined to include nectarine and peach (*Prunus persica*) on the list in § 174.27(a)(1) on the basis of information received from expert consultations. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to introgress into a population of a wild or weedy relative or a naturalized population of the species and what effect such introgression might have. Specifically, the experts indicated that natural hybrids may be able to form with some other stone fruit trees (Ref. 42). However, if such trees are likely to be found in commercial cultivation, natural hybrids would not necessarily be expected in areas outside of managed orchards. Regarding whether *Prunus persica* is a weedy species, three of the four experts mentioned that nectarines and peaches are able to form feral populations (Ref. 42). Nevertheless, three of the four experts indicated that they believed it would be unlikely that *Prunus persica*'s weedy tendencies, if any, would be exacerbated if it acquired transgenic resistance to one or more viruses. One expert said, "Generally the viruses are not the limiting factor to the establishment of feral peaches. The limiting factors are fungal and bacterial diseases that kill the plants before they can reproduce" (Ref. 42). The fourth expert said, "I would expect that the acquisition of virus resistance would enhance the spread of feral populations but would suggest that other causes of death, such as peach tree short life, bacterial canker and Armillaria Root Rot, are likely to be a more significant limitation to the spread and longevity of a feral nectarine tree" (Ref. 42).

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EPA believes that more information about olive (*Olea europaea*) is needed to address issues raised during expert consultation. Two experts indicated that hybridization with a wild or weedy relative has not been documented in the United States (Ref. 42). Both of these experts indicated that olive can naturalize. However, they disagreed about

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the frequency with which this is likely to occur. One expert suggested olive frequently forms reproducing and sustaining populations in non-crop areas and that it was "highly likely" that olive would become feral or easily spread into non-crop areas if it acquired transgenic resistance to one or more viruses because "*O. europaea* seeds are very viable and dispersed by rodents" (Ref. 42). However, another said, "It is highly unlikely that olives would become strongly feral or widely spread because the seeds are infrequently spread far from the tree, have a low reproduction rate due to poor seed germination and have a high rate of feral seedling mortality. Further, as a slow growing tree olives do not spread rapidly" (Ref. 42). The 2005 SAP also commented on including olives in the list of plants in § 174.27(a)(1). They noted olives have reportedly formed "feral olive infestations in the Channel Islands National Park, and in oak woodlands and forest on Sonoma Valley and Davis, CA. In California, olive is 'considered an invasive exotic' that 'compete[s] with native flora' (personal communication)" (Ref. 42). EPA believes that before olive could be added to the list of plants in § 174.27(a)(1), the Agency would need information to resolve the question of how weedy olive is in the United States and the effect virus resistance would have on any feral populations of olive that could acquire a PVCP-PIP from cultivated olive.

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EPA has received one response from a parsley expert suggesting that parsley (*Petroselinum crispum*) meets the requirements for inclusion on the list in § 174.27(a)(1). This consultation indicates that parsley meets the three conditions outlined above by the SAP: it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make parsley weedy or invasive. The breeder noted that parsley could form viable hybrids with feral populations of parsley, but "parsley populations are generally quite short-lived away from cultivation and typically are not self-sustaining" (Ref. 42). He also noted, "I would not expect parsley to become more easily spread with the acquisition of virus resistance. Although I'm aware that parsley is a host to celery mosaic virus and carrot motley dwarf, I have not known these viruses to be common limiting factors in parsley growth or reproduction, at least not here at our genebank in Iowa. Fungal diseases and insects are much more important" (Ref. 42). EPA is seeking public comment on this determination because the Agency desires a more robust response base.

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EPA is inclined to include petunia (*Petunia* spp.) on the list in § 174.27(a)(1) on the basis of information received from consultations with petunia experts. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the weedy characteristics of petunia and the likelihood that acquired virus resistance could cause petunia to become feral or easily spread into non-crop areas. The experts indicated that this genus does not form viable hybrids in nature with wild or weedy relatives in the United States. However, two of the three experts indicated that petunia has formed reproducing and sustaining populations in non-crop areas while noting that such populations have not required weed management activity. All three experts indicated that acquired virus resistance is unlikely to change the status quo. However, one noted that, "as viruses affect petunia vigor, resistance might conceivably increase the odds" (Ref. 42).

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EPA is inclined to include pistachio (*Pistacia vera*) on the list in 174.27(a)(1) on the basis of information received from two expert consultations. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to introgress into a population of a wild or weedy relative or a naturalized population of the species and what the impact of acquired virus resistance is likely to be. Specifically, the experts indicated several crosses have been reported in the literature, suggesting "that potentially *P. vera* genes can eventually be transmitted to other species in the form of gene flow." However, hybrids are only rarely formed as "they are isolated phenologically…." Nevertheless, one expert also indicated, "There are a lot of unknowns in the phenology and cross-compatibility of different species of pistachio" (Ref. 42). Both experts indicated that ferality in pistachio is rare. One suggested it was not possible to say what the likelihood would be that pistachio would become feral or easily spread into non-crop areas if it acquired transgenic virus resistance. However the other said, "It is very unlikely pistachio would be widely feral as the primary method of spread, drop from the tree, results in a large percentage (>95%) of the nuts degrading, so they do not sprout. Further, the nuts do not go a long distance when they drop, localizing spread if sprouting does occur. Finally, if birds do remove a nut with a viable embryo from the tree they generally destroy it by eating…" (Ref. 42).

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EPA is inclined to include plum (*Prunus domestica*) on the list in § 174.27(a)(1) on the basis of information received from expert consultations. However, EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to introgress into a population of a wild or weedy relative or a naturalized population of the species. Specifically, the experts indicated that several native plum species occur in the United States. However, one indicated that because "*P. domestica* is a hexaploid, it would not cross with native *Prunus* plum species, which are all diploid" (Ref. 42). In addition, if any hybrids between cultivated plum and wild American plum species did occur, they "would not be fertile because of the chromosome number difference." EPA thus believes that the risk of introgressing a PVCP-PIP into a wild or weedy population through gene transfer in the United States is very low. Regarding whether plum is a weedy species, one expert mentioned that although he had not personally observed it, he "heard from others that domestica… [is] found naturalized particularly in New England and Oregon. Some of these species tend to be easily spread by root suckers, and are better able to compete as weeds. Likely they only survive on roadsides and unmanaged areas, and could be easily killed if desired" (Ref. 42). Nevertheless, all three of the experts indicated that they believed it would be unlikely that plum's weedy tendencies, if any, would be exacerbated if it acquired transgenic resistance to one or more viruses. According to one expert, "I doubt viruses are the only thing which restricts domestica from spreading more than it already has" (Ref. 42). According to another, "Currently virus diseases are not the most important limiting diseases for plum in the U.S. Other fungal and bacterial diseases are the limiting factors and cause death of uncared for commercial plums. Therefore transgenic plums with virus resistance would still be very susceptible to these limiting fungal and bacterial diseases" (Ref. 42).

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EPA has received one response from a spinach expert suggesting that spinach (*Spinacia oleracea*) meets the requirements for inclusion on the list in § 174.27(a)(1). This consultation indicated that spinach meets the three conditions outlined above by the SAP: it does not have wild or weedy relatives in the United States with which it can form viable hybrids in nature, it is not currently weedy or invasive in the United States, and there is no reason to believe that acquisition of virus resistance would make spinach weedy or invasive. The expert noted, "Transgenic viral resistance alone probably would not make spinach survive wild conditions, because there are other fungus (e.g. downy mildew, Stemphylium leaf spot) diseases and bacterial diseases (e.g. bacterial leaf spot), as well as drought resistance and competing ability issues" (Ref. 42). EPA is seeking public comment on this determination because the Agency desires a more robust response base.

EPA believes that more information about taro (*Colocasia esculenta*) is needed to address issues raised by expert consultation. For example, although experts knew of no weedy relatives with which taro might cross, "crossing is theoretically possible among all of the taros" (Ref. 42). One expert indicated that "taro can flower naturally in places such as Kula in Maui, Hawaii. The climate there allows taro to flower naturally, whereas in other places it is often necessary to induce flowering with hormone applications. Furthermore, hybrids made by cross-fertilization are viable. It is entirely possible for taro to survive in the wild in tropical and subtropical climates. Most taros would succumb because taro has been cultivated for so long that it is mostly dependent on humans to compete with many weeds. By itself it is almost always out-competed by weeds and dies out. But theoretically it can survive, it can cross-pollinate and form viable progeny" (Ref. 42). Regarding whether taro is known to become feral or easily spread in non-crop areas, one expert said, "YES, but only in favorable conditions of adequate warmth and moisture." Another expert indicated that "taro is considered an invasive species in certain places (Florida)" (Ref. 42). Regarding whether acquired transgenic resistance to one or more viruses could change taro in this respect, the experts disagreed. One expert said, "It is highly unlikely that taro with acquired transgenic resistance would spread to non-crop areas because the probability of crossing is extremely small. Through vegetative propagation it will require man intervention just as non-transgenic plants." Another expert said, "Taro has many pests, including viruses, that restricts [sic] its ability to compete with more weedy plant species. Resistance to any of these pests would increase its competitiveness but this is not likely to turn taro into a weed problem." However, the third expert said, "With resistance to one or more virus diseases, taro would become hardier. That is the reason for breeders to go to the trouble of developing disease-resistant plants. A hardier taro is more likely to be successful and survive as an escaped cultivated species. It has already been seen that taro has become feral in certain parts of Florida. With added resistance, it would be more likely to survive in the wild, provided that resistance gives it some advantage. In other words, if the virus disease is important, resistance is valuable. In Thailand, the taro plants that one can find along roadsides (feral) possess a high degree of resistance to taro leaf blight, the most destructive disease of cultivated taro there. Those that don't possess resistance don't stand much of a chance to survive on their own" (Ref. 42). EPA believes that before taro could be added to the list of plants in § 174.27(a)(1), the Agency would need information to evaluate the likelihood that feral populations of taro could acquire a PVCP-PIP from cultivated taro and to

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evaluate whether acquisition of virus resistance is likely to increase taro's likelihood of forming feral populations.

EPA believes that more information about tomato (*Solanum lycopersicum*) is needed to address issues raised by several experts that EPA consulted. For example, three of four experts indicated that tomato is able to form viable hybrids in nature in the United States with its putative progenitor *Solanum lycopersicum* var. *cerasiforme*. These experts indicated the hybrids formed are fertile, self-compatible, and freely intercross due to highly compatible phenology. However, a third expert indicated that "[a]lthough crosses can occur between wild species and cultivated tomato, usually with human intervention, the direction of the cross is such that the wild species has to be the male parent…. If the cultivated tomato has the transgene, transfer to wild species via pollen will not happen" (Ref. 42). EPA is not however interested solely in whether transfer occurs via pollen, but whether a transgene could introgress into a wild population through a hybrid intermediate. Three of four experts also indicated that tomato is able to form feral populations in the United States (including Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa), although one expert pointed out that neither virus-resistant cultivars nor resistant wild relatives have demonstrated a greater propensity to become feral, suggesting that acquisition of a PVCP-PIP may not exacerbate whatever weedy tendencies exist in tomato. However, another expert suggested that this question would have to be tested in the field under controlled conditions. EPA believes that before tomato could be added to the list of plants in § 174.27(a)(1), the Agency would need information to evaluate the effect of virus resistance on any wild or weedy populations of tomato that could acquire a PVCP-PIP from cultivated tomato and to evaluate whether acquisition of virus resistance is likely to exacerbate tomato's weedy tendencies.

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EPA believes that more information about watermelon (*Citrullus lanatus*) is needed to address issues raised by expert consultation. For example, experts indicated that watermelon is able to cross with *C. lanatus* var. *citroides*. Moreover, one expert indicated hybrids made by cross-fertilization are sexually fertile and demonstrate "[m]ore vigor compared with cultivated watermelon (*C. lanatus* var. *lanatus*)" (Ref. 42). Regarding whether watermelon is known to become feral or easily spread in non-crop areas, one expert indicated that escaped plants are able to form reproducing and sustaining populations in non-crop areas, although this occurs rarely and has not required weed management activity outside of crop areas (Ref. 42). Regarding whether acquired transgenic resistance to one or more viruses could change watermelon in this respect, one expert indicated this was "[u]nlikely. Watermelons have few viruses that kill the plant or decrease its reproductive activity. Therefore, gaining virus resistance will not likely increase it's [sic] reproductive success in feral populations" (Ref. 42). Another expert said, "Virus pressure would likely be far less in feral populations than in cultivated fields due to differences in time of germination, rate of growth, population density, [and] reduced numbers of aphid vectors" (Ref. 42). EPA believes that before watermelon could be added to the list of plants in § 174.27(a)(1), the Agency would need information to evaluate the likelihood that wild populations of *C. lanatus* var. *citroides* or feral populations of *C. lanatus* var. *lanatus* could acquire a PVCP-PIP from cultivated watermelon and what effect this acquisition might have.

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EPA believes that more information about wishbone flower (*Torenia* spp.) is needed to address issues raised by expert consultation. EPA is seeking any information from the public that would enable the Agency to complete its assessment of the potential for a PVCP-PIP to enhance the potential of species in this genus to naturalize. All three experts consulted indicated that *Torenia* species do not form viable hybrids in nature with wild or weedy relatives in the United States. However, all indicated that *Torenia* has naturalized in certain areas of the United States. One expert said, "*Torenia fournieri* has been reported to naturalize by seed in Florida and Louisiana, but it is not clear to what extent. I personally have observed re-seeding in garden settings. Given the rising popularity of Torenia in American horticulture, there is probable cause for concern in the deep south, California and Hawaii. However, the species in cultivation are heat sensitive and moisture-demanding, which would probably limit the extent to which they can naturalize" (Ref. 42). Expert consultations also suggest that not enough information is known about the potential of virus resistance to affect the plant's weedy tendencies. One expert said, "I do not know to what extent viruses impact *Torenia fournieri*. It is conceivable that viral resistance could increase fecundity" (Ref. 42).

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EPA is not proposing to include celery (*Apium graveolens*), kiwi (*Actinidia* spp.), or okra (*Abelmoschus esculentus*) on the list in § 174.27(a) because the Agency was unable to complete any expert consultations on these crops. EPA is therefore seeking information from the public to address whether such crops could qualify for inclusion on the list.

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EPA also requests comment on the weediness potential of squash (*Cucurbita pepo*) and any wild or weedy relatives in the United States that could acquire a PVCP-PIP from cultivated squash through gene flow.

2. EPA requests comment on the Agency's options for the weediness criterion in § 174.27(a)(2) discussed in Unit III.C.2.iii. Specifically, the Agency is considering whether it is more appropriate to evaluate the potential for a crop to form "viable hybrids" or "viable, fertile hybrids" in nature with a wild or weedy relative.

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In addition, EPA is considering whether it is necessary to evaluate whether the plant containing the PIP is unlikely to establish weedy or invasive populations outside of agricultural fields in the United States even if the plant contains a PVCP-PIP, assuming that the plant has no wild or weedy relatives in the United States with which it can form viable hybrids in nature and it is not a weedy or invasive species outside of agricultural fields in the United States.

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EPA also requests comment on language for the criterion in § 174.27(a)(2) (e.g., such as under option four) that would allow EPA to broadly consider the effect that virus resistance might have on wild or weedy plant populations that could acquire the PVCP-PIP. Under such an approach, the individual determinations that the Agency would make would likely require data to be generated that would not normally occur as a routine part of product development (but may be developed for a review by USDA/APHIS). Such determinations are likely to involve similar amounts of effort as registration reviews, but they would provide a means whereby a PVCP-PIP could be exempted even if used in a plant that has wild or weedy relatives in the United States. The Agency requests

commenters to indicate how controversial individual determinations using such language as under option 4 are likely to be, as the Agency would like to have an exemption procedure that requires only one public notice (see Unit III.A.2.).

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3. EPA requests comment on the merits of incorporating the use of biocontainment and/or bioconfinement techniques into § 174.27(a), such that PVCP-PIPs deployed in tandem with such technology could be determined to meet the weediness criterion. Please see the discussion of this option in Unit III.C.3., which articulates several issues associated with such an option and suggests regulatory language that might be used.

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4. EPA requests comment on the Agency's use of the term "weedy." EPA uses the term in two different contexts: in "wild or weedy relatives" and in "weedy or invasive species." However, the Agency notes that the term has a different meaning in each context. When discussing a "wild or weedy relative," EPA considers weedy plants to be those with the characteristics of weeds, i.e., those that are considered undesirable, unattractive, or troublesome, especially when growing where they are not wanted. However, when discussing "weedy or invasive species," EPA considers a weedy species to be a species that is an aggressive competitor in natural ecosystems. EPA recognizes that it would be better to have a single definition of the term "weedy," but the Agency believes both meanings of the term "weedy" are in common, scientific usage. In addition, the Agency is not aware of a term other than "wild or weedy relative" that would encompass all plants that grow outside of agricultural fields, or a term other than "weedy or invasive species" that would encompass all of the plants that are problematic from a management perspective. EPA would be particularly interested in alternative suggestions to describe each of these situations and thus enable the Agency to avoid using two different meanings for the word "weedy."

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5. EPA requests comment on whether the viral interactions criterion in § 174.27(b)(1)(i) could be expanded to read "the viral pathotype used to create the PVCP-PIP has naturally infected plants in the United States *or other parts of North America* and naturally infects plants of the same species as those containing the PVCP-PIP." EPA recognizes that viruses are likely to move freely across political boundaries. Thus, limiting this criterion to viruses that have naturally infected plants "in the United States or other parts of North America" may be most appropriate limitation for avoiding the introduction of sequences from an exotic virus into the United States through creation of a PVCP-PIP.

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6. EPA requests comment on whether it is necessary for the Agency to address viral interactions, i.e., recombination, as articulated in § 174.27(b), in order for the Agency to conclude that a PVCP-PIP is low risk. EPA requests commenters to indicate whether their comments apply to RNA viruses, DNA viruses, or both. The Agency notes that a large number of PVCP-PIPs are likely to meet § 174.27(b) as proposed. EPA therefore requests commenters who believe § 174.27(b) is unnecessary to focus their remarks on why those PVCP-PIPs that *do not meet the conditions of proposed § 174.27(b)* would pose low risk with respect to recombination rather than addressing the average risk associated with PVCP-PIPs as a whole.

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For the PVCP-PIPs that would only qualify for an exemption without the limitations provided by § 174.27(b), EPA does not believe the Agency can conclude low risk with respect to recombination (as the Agency must do in order to remove § 174.27(b) entirely) because the 2004 and 2005 SAPs have identified specific instances where this general conclusion may not hold. Nevertheless, EPA is considering removing this criterion in whole or in part if the Agency receives information suggesting that such factors as articulated and as incorporated into § 174.27(b) are unnecessary for concluding a particular PVCP-PIP is low risk. For example, the Agency notes that the current global movement of goods and people likely results in the at least occasional transport of plant viruses great distances from their original geographic distribution in spite of governmental efforts to limit their movement. In such a context, the Agency questions the relevance of requiring as a condition of exemption that the viral pathotype used to create the PVCP-PIP has naturally infected plants in the United States.

7. EPA requests comment on whether the protein production criterion in § 174.27(c)(1)(i) could be modified to encompass other types of PVCP-PIP constructs that mediate resistance based on PTGS. According to today's proposal, any such constructs other than those inserted only in an inverted repeat orientation or lacking a start codon would be reviewed by the Agency for lack of protein production under § 174.27(c)(2). However, if the Agency could identify additional types of constructs that would present reasonable assurance that no protein would be produced in any plant tissues at any point in the plant's developmental cycle, including if PTGS were to be suppressed, such constructs could be included under § 174.27(c)(1)(i) and would not require Agency review to verify that no protein would be produced.

8. EPA requests comment on whether the Agency could extend the proposed exemption (including regulatory text and rationale as written) to other PIPs that are based on any plant virus gene that confers virus resistance when no protein is produced from the inserted virus sequence because it is inserted only in an inverted repeat orientation and/or it lacks an initiation codon for protein synthesis. The 2005 SAP noted that "[o]ther PIPs conferring virus resistance should be evaluated similarly as are the PVCP-PIPs, if the PIPs mode of action is via PTGS" (Ref. 11). However, the Panel also mentioned several risk concerns associated with specific virus proteins. The Agency therefore concluded that PTGS was a necessary but not sufficient condition for expanding the exemption to other types of virus gene-based PIPs given that protein can be produced under certain circumstances from many constructs that employ PTGS, and the Agency does not currently have sufficient information to conclude that such protein would pose low risk to the environment. In the case of the two types of inserts described above, the 2005 SAP indicated that it could be "safely determined" that no protein would ever be produced from such constructs (Ref. 11), and they would meet § 174.27(b) and (c). Section 174.27(a) would be evaluated as it is evaluated for PVCP-PIPs given that the relevant consideration would be the virus-resistant phenotype of the plant rather than the means by which the trait is conferred. EPA thus believes that the criteria in today's proposed exemption address all relevant risk considerations for PIPs based on any plant virus gene when no protein is produced from the inserted virus sequence. EPA is therefore inclined to expand the exemption to include PIPs based on any viral gene that confers virus resistance if the PIP meets § 174.27(a) and no protein is produced from the

**Deleted:** The Agency notes that the 2005 SAP concluded that "the likelihood for 'novel' interactions is very low, and the environmental concerns that might result from using PVCP-PIPs in the United States… is lower than that which occurs naturally from mixed virus infections" (Ref. 11). In addition, "it was repeatedly stated that the consequences of any recombination event are minimal. This conclusion was based on the fact that nearly every plant on the planet is harboring multiple virus infections with both closely related and taxonomically distinct viruses, with essentially no new viruses emerging with substantially different properties and causing wide pandemics or undesirable environmental effects" (Ref. 11). In spite of such comments, EPA's proposal retains § 174.27criterion (b) because of the overall context of the Panel's response which articulated several factors (discussed in Unit III.E.2.vii) that should be considered when evaluating recombination.

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**Deleted:** When developing comments, the Agency requests commenters to take into account that a large number of PVCP-PIPs are likely to meet criterion (b) as proposed, supported by the rationale developed in Unit III.E.2. EPA believes criterion (b) is consistent with the comments of the 2005 SAP that "the likelihood for 'novel interactions' is very low" (Ref. 11), because the Agency believes this conclusion holds only when considering the whole set of PVCP-PIPs that are likely to be developed. EPA does not believe the Agency can make this conclusion about all PVCP-PIPs that would qualify for an exemption without criterion (b) (as the Agency must do in order to remove criterion (b) entirely) because the 2004 and 2005 SAPs have identified specific instances where this general conclusion may not hold. The Agency therefore requests commenters who believe that criterion (b) is unnecessary to ensure low risk to focus their remarks on why those PVCP-PIPs that *do not meet the conditions of proposed criterion (b)* would pose low risk with respect to recombination rather than addressing the average risk associated with PVCP-PIPs as a whole. ¶

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inserted virus sequence because it is inserted only in an inverted repeat orientation and/or it lacks an initiation codon for protein synthesis.

9. EPA requests comment on the alternative approach the Agency is considering for exempting marker genes that are used as inert ingredients with PIPs under which NPTII, GUS, and PMI would be exempt from FIFRA when used as inert ingredients with any exempt PIP, regardless of the plant in which they are expressed (as discussed in Unit IV.).

10. EPA requests comment on the possibility of developing an Agency-determined approach for exempting inert ingredients under FIFRA. Under this approach, EPA would propose new language at 40 CFR 174.21(c) that would enable the Agency to review inert ingredients on a case-by-case basis to determine whether they meet the standard established for inert ingredients in 40 CFR part 174 subpart X—List of Approved Inert Ingredients. EPA is considering such a procedure to ensure that a low-risk PVCP-PIP that otherwise meets the conditions for exemption at § 174.21 would not require a FIFRA registration solely due to the presence of an inert ingredient that may prove to be low risk upon review. The only alternative to registration for such a PVCP-PIP would be to add the inert ingredient to the list through rulemaking under FIFRA section 25(b), such that the PVCP-PIP could be exempted. Rulemaking would take considerably longer than an Agency determination procedure like that described in today's proposal for other exemption criteria.

The criteria that EPA is considering for determining whether an inert ingredient would be exempt under an Agency determination are:

i. The inert ingredient is non-toxic to humans and animals and does not produce a toxic substance,

ii. The inert ingredient is non-allergenic, and

iii. If the inert ingredient is an antibiotic resistance gene or marker protein, therapy with antibiotics would not be compromised even if the gene were to be transferred from plants to microorganisms in the gut of man or animal, or in the environment.

11. EPA requests comment on the Agency's assumption in the economic analysis for this proposed rule that the estimated number of PVCP-PIPs submitted for regulatory review will be the same per year over the next 10 years. EPA assumed a uniform distribution given that the Agency lacks reliable information on which to base a more complex distribution pattern. EPA is particularly interested in any data or information supporting a different assumption for the economic analysis.

12. EPA requests comment on the usefulness of a guidance document that would provide a simplified description of the final rule. EPA intends to develop such a document and is interested to know what specific content the public would find most helpful.

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## IX. Content of Official Record

EPA has established an official record for this rulemaking. The official record includes all information considered by EPA in developing this proposed rule including documents specifically referenced in this action, any public comments received during an applicable comment period, and any other information related to this action, including any information claimed as CBI and any information received in any of the related dockets mentioned below. This official record includes all information physically located in the dockets described in the following paragraph, as well as any documents that are referenced in the documents in the dockets. The public version of the official record does not include any information claimed as CBI.

The complete official record for this rulemaking includes:

The docket identified by the docket control number OPP-300370 for the document entitled “Proposed Policy: Plant-Pesticides Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act” (59 FR 60496, November 23, 1994)(FRL–4755–2).

The docket identified by the docket control number OPP-300369 for the document entitled “Plant-Pesticides Subject to the Federal Insecticide, Fungicide and Rodenticide Act; Proposed Rule” (59 FR 60519, November 23, 1994)(FRL–4755–3).

The docket identified by the docket control number OPP-300368 for the document entitled “Plant-Pesticides; Proposed Exemption From the Requirement of a Tolerance Under the Federal Food, Drug, and Cosmetic Act” (59 FR 60535, November 23, 1994)(FRL–4758–8).

The docket identified by the docket control number OPP-300371 for the document entitled “Plant-Pesticides; Proposed Exemption From the Requirement of a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Nucleic Acids Produced in Plants” (59 FR 60542, November 23, 1994)(FRL–4755–5).

The docket identified by the docket control number OPP-300367 for the document entitled “Plant-Pesticides; Proposed Exemption From the Requirement of a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Viral Coat Proteins Produced in Plants” (59 FR 60545, November 23, 1994)(FRL–4755–4).

The docket identified by the docket control number OPP-300370A for the document entitled “Plant-Pesticide Subject to the Federal Insecticide, Fungicide, and

Rodenticide Act and the Federal Food, Drug, and Cosmetic Act; Reopening of Comment Period" (61 FR 37891, July 22, 1996)(FRL–5387–4).

The docket identified by the docket control number OPP-300368A for the document entitled "Plant-Pesticides; Supplemental Notice of Proposed Rulemaking" (62 FR 27132, May 16, 1997)(FRL–5717–2).

The docket identified by the docket control number OPP-300371A for the document entitled "Plant-Pesticides; Nucleic Acids; Supplemental Notice of Proposed Rulemaking" (62 FR 27142, May 16, 1997)(FRL–5716–7).

The docket identified by the docket control number OPP-300367A for the document entitled "Plant-Pesticides; Viral Coat Proteins; Supplemental Notice of Proposed Rulemaking" (62 FR 27149, May 16, 1997)(FRL–5716–6).

The docket identified by the docket control number OPP-300369A for the document entitled "Plant-Pesticides, Supplemental Notice of Availability of Information" (64 FR 19958, April 23, 1999)(FRL–6077–6).

The docket identified by the docket control number OPP-300369B for the document entitled "Regulations Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants (Formerly Plant-Pesticides)" (66 FR 37772, July 19, 2001)(FRL–6057–7).

The docket identified by the docket control number OPP-300368 for the document entitled "Exemption From the Requirement of a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Residues Derived Through Conventional Breeding From Sexually Compatible Plants of Plant-Incorporated Protectants (Formerly Plant-Pesticides)" (66 FR 37830, July 19, 2001)(FRL–6057–6).

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The docket identified by the docket control number OPP-300371 for the document entitled "Exemption From the Requirement of a Tolerance Under the Federal Food, Drug, and Cosmetic Act for Residues of Nucleic Acids that are Part of Plant-Incorporated Protectants (Formerly Plant-Pesticides)" (66 FR 37817, July 19, 2001)(FRL–6057–5).

The docket identified by the docket control number OPP-300370B for the document entitiled "Plant-Incorporated Protectants (Formerly Plant-Pesticides), Supplemental Proposal" (66 FR 37855, July 19, 2001)(FRL–6760–4).

The docket identified by the docket control number EPA-HQ-OPP-2006-0643 for the companion document entitled "Exemption from the Requirement of a Tolerance under the Federal Food, Drug, and Cosmetic Act for Residues of Plant Virus Coat Proteins that are Part of a Plant-Incorporated Protectant (PVC-Proteins)" (FRL–8100–5) published elsewhere in this issue of the **Federal Register**.

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The docket identified by the docket control number EPA–HQ–OPP–2006–0642 for this document (FRL–8100–7).

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Also included in the complete official record are:

1. Public comments submitted in response to the proposals and supplemental documents cited in the above paragraph.

2. Reports of all meetings of the Biotechnology Science Advisory Committee and the FIFRA Scientific Advisory Panel pertaining to the development of this proposed rule.

3. The Economic Analysis for this proposed rule and supporting documents.

4. Support documents and reports.

5. Records of all communications between EPA personnel and persons outside EPA pertaining to the proposed rule. (This does not include any inter- and intra-agency memoranda, unless specifically noted in the indices of the dockets).

6. Published literature that is cited in this document.

## X. Statutory and Executive Order Reviews

### *A. Executive Order 12866*

Pursuant to Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), the Office of Management and Budget (OMB) has determined that this is a "significant regulatory action" because it may raise potentially novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order. Therefore, this action was submitted to OMB for review, and changes made during that review have been documented in the docket.

In addition, EPA has prepared an economic analysis of the impacts related to this proposed action. The economic analysis evaluates the quantifiable benefits of exempting PVCP-PIPs from FIFRA requirements (40 CFR part 174) and discusses the non-quantifiable benefits of this action. This economic analysis is contained in a document entitled "Economic Analysis for Proposed Exemption Under the Federal Insecticide, Fungicide, and Rodenticide Act for Certain Plant-Incorporated Protectants Derived from a Plant Viral Coat Protein Gene (PVCP-PIPs)" (called here "the EA"). This document is available in the docket and is briefly summarized in Unit V.

### *B. Paperwork Reduction Act*

Pursuant to the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, 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, or is otherwise required to submit the specific information by a statute. The OMB control numbers for EPA's regulations codified in Chapter 40 of the CFR, after appearing in the preamble of the final rule, are further displayed either by publication in the **Federal Register** or by other appropriate means, such as on the related collection instrument or form, if applicable. The display of OMB control numbers in certain EPA regulations is consolidated in a list at 40 CFR 9.1.

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The information collection requirements contained in this proposed rule have been submitted to OMB for review and approval under the PRA in accordance with the procedures at 5 CFR 1320.11. The burden and costs related to the information collection requirements contained in this rule are described in an addendum to a currently approved Information Collection Request (ICR) identified as EPA ICR No. 1693.04 (OMB number 2070-0142).

As defined in the PRA, "burden" means the total time, effort, or financial resources expended by persons to generate, maintain, retain, or disclose or provide information to or for a Federal agency. This includes the time needed to review instructions; develop, acquire, install, and utilize technology and systems for the purposes of collecting, validating, and verifying information, processing and maintaining information, and disclosing and providing information; adjust the existing ways to comply with any previously applicable instructions and requirements; train personnel to be able to respond to a collection of information; search data sources; complete and review the collection of information; and transmit or otherwise disclose the information.

This proposed rule includes information collection requirements of developers who wish to exempt PVCP-PIPs under the provisions of the proposed rule. Developers self-determining their exemption status will have to develop and maintain records supporting their determination and report their determination to EPA. Developers relying on Agency determination of exemption status will have to develop the information needed for the Agency determination and submit it to EPA. The Agency has estimated that this information collection has an estimated burden of 21.5 hours per response for developer-determined exemptions and 23.5 hours per response for Agency-determined exemptions. EPA estimates that there will be one submission of each type per year for a total annual respondent burden of 45 hours.

Direct your comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including the use of automated collection techniques, to EPA using the public docket that has been established for this proposed rule (Docket ID No. EPA-HQ-OPP-2006-0642). In addition, send a copy of your comments about the ICR to OMB at: Office of Information and Regulatory Affairs, Office of Management and Budget, 725 17th St., NW., Washington, DC 20503, Attention: Desk Office for EPA ICR No. 2070-0142. Since OMB is required to complete its review of the ICR between 30 and 60 days after [*insert date of publication in the* **Federal Register**], please submit your ICR comments for OMB consideration to OMB by [*insert date 30 days after date of publication in the* **Federal Register**].

The Agency will consider and address comments received on the information collection requirements contained in this proposal when it develops the final rule.

*C. Regulatory Flexibility Act*

The Regulatory Flexibility Act (RFA) generally requires an agency to prepare a regulatory flexibility analysis of any rule subject to notice and comment rulemaking requirements under the Administrative Procedure Act or any other statute unless the

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agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Small entities include small businesses, small organizations, and small governmental jurisdictions.

For purposes of assessing the impacts of today's rule on small entities, small entity is defined as: (1) a small business according to the small business size standards established by the U.S. Small Business Administration (SBA), which in this case is a pesticides and agricultural chemical producer (NAICS code 325320) with fewer than 500 employees; a crop producer (NAICS code 111) with less than $750,000 in revenues; a college, university, or professional school (NAICS code 611310) with annual revenues less than $6.5 million; or an entity in research and development in the physical, engineering, and life sciences (NAICS code 54171) with fewer than 500 employees; (2) a small governmental jurisdiction that is a government of a city, county, town, school district or special district with a population of less than 50,000; and (3) a small organization that is any not-for-profit enterprise which is independently owned and operated and is not dominant in its field.

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After considering the economic impacts of today's rule on small entities, I certify that this action will not have a significant economic impact on a substantial number of small entities.

In determining whether a rule has a significant economic impact on a substantial number of small entities, the impact of concern is any significant adverse economic impact on small entities, since the primary purpose of the regulatory flexibility analyses is to identify and address regulatory alternatives "which minimize any significant economic impact on of the proposed rule on small entities" (5 U.S.C. sections 603 and 604). Thus, an agency may certify that a rule will not have a significant economic impact on a substantial number of small entities if the rule relieves regulatory burden or otherwise has a positive economic effects on all of the small entities subject to the rule.

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This proposed rule will not have a significant economic impact on a substantial number of small entities. The factual basis for this determination is contained in the EA accompanying this rule. Specifically, this rule will generate savings by exempting PVCP-PIPs with a low probability of risk from FIFRA requirements. Given the overall potential savings attributed to this rule, the Agency concludes that this proposed action will not result in adverse economic impacts, regardless of the size of the firm currently developing and testing PVCP-PIPs or planning to develop and test PVCP-PIPs. Today's action relieves regulatory burden. Nevertheless, the Agency continues to be interested in the potential impacts of the proposed rule on small entities and welcomes comments on issues related to such impacts.

*D. Unfunded Mandates Reform Act*

Title II of the Unfunded Mandates Reform Act of 1995 (UMRA), Public Law 104-4, establishes requirements for Federal agencies to assess the effects of certain regulatory actions on State, local, and tribal governments and the private sector. Under section 202 of the UMRA, EPA generally must prepare a written statement, including a cost-benefit analysis, for final and proposed rules with "Federal mandates" that may

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result in expenditures to State, local, and tribal governments, in the aggregate, or to the private sector, of $100 million or more in any one year. Before promulgating an EPA rule for which a written statement is needed, section 205 of the UMRA generally requires EPA to identify and consider a reasonable number of regulatory alternatives and adopt the least costly, most cost-effective or least burdensome alternative that achieves the objectives of the rule. The provisions of section 205 do not apply when they are inconsistent with applicable law. Moreover, section 205 allows EPA to adopt an alternative other than the least costly, most cost-effective or least burdensome alternative if the Administrator publishes with the final rule an explanation why that alternative was not adopted. Before EPA establishes any regulatory requirements that may significantly or uniquely affect small governments, including tribal governments, it must have developed under section 203 of the UMRA a small government agency plan. The plan must provide for notifying potentially affected small governments, enabling officials of affected small governments to have meaningful and timely input in the development of EPA regulatory proposals with significant Federal intergovernmental mandates, and informing, educating and advising small governments on compliance with the regulatory requirements.

EPA has determined that this action does not contain a Federal mandate that may result in expenditures of $100 million or more for State, local or tribal governments, in the aggregate, or on the private sector in any one year. The analysis of the cost savings associated with this action are described in Unit V. of this preamble. The requirements of sections 202, 203, 204 or 205 of UMRA which relate to regulatory requirements that might significantly or uniquely affect small governments and to regulatory proposals that contain a significant Federal intergovernmental mandate, respectively, also do not apply to today's rule because the rule affects only the private sector, i.e., persons field testing such as universities, multinational companies, biotechnology companies, chemical companies, seed companies; persons selling and distributing such as multinational companies, biotechnology companies, chemical companies, seed companies; and persons using PVCP-PIPs such as farmers.

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*E. Executive Order 13132: Federalism*

Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999) requires EPA to develop an accountable process to ensure "meaningful and timely input by State and local officials in the development of regulatory policies that have federalism implications." "Policies that have federalism implications" is defined in the Executive Order to include regulations that 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." Under section 6 of Executive Order 13132, EPA may not issue a regulation that has federalism implications, that imposes substantial direct compliance costs, and that is not required by statute, unless the Federal government provides the funds necessary to pay the direct compliance costs incurred by State and local governments, or EPA consults with State and local officials early in the process of developing the proposed regulation. EPA also may not issue a regulation that has federalism implications and that preempts State law, unless the

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Agency consults with State and local officials early in the process of developing the proposed regulation.

This proposed rule does not have federalism implications. 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, as specified in Executive Order 13132. The primary result of this action is to exempt certain PVCP-PIPs from most FIFRA requirements. Thus, the requirements of section 6 of the Executive Order do not apply to this rule.

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

Executive Order 13175, *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 9, 2000), requires EPA to develop an accountable process to ensure "meaningful and timely input by tribal officials in the development of regulatory policies that have tribal implications." "Policies that have tribal implications" is defined in the Executive order to include regulations that have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Under Executive Order 13175, EPA may not, to the extent practicable and permitted by law, issue a regulation that has tribal implications, that imposes substantial direct compliance costs, and that is not required by statute, unless, among other things, the Federal government provides the funds necessary to pay the direct compliance costs incurred by tribal governments, and EPA consults with State and local officials early in the process of developing the regulation. Similarly, to the extent practicable and permitted by law, EPA may not issue a regulation that has tribal implications and that preempts tribal law unless EPA, among other things, consults with tribal officials early in the process of developing the regulation.

EPA has concluded that this rule does not have tribal implications in that it does not have substantial direct effects as specified in the Executive order. In particular, EPA notes that this rule does not impose either direct or indirect compliance costs on tribal governments. In this action, EPA is proposing to exempt certain PVCP-PIPs from most FIFRA requirements. This is only expected to affect the private sector, i.e., persons field testing such as universities, multinational companies, biotechnology companies, chemical companies, seed companies; persons selling and distributing such as multinational companies, biotechnology companies, chemical companies, seed companies; and persons using PVCP-PIPs such as farmers who sell and distribute such products. Thus, Executive Order 13175 does not apply to this rule.

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

Pursuant to Executive Order 13045, *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997), for any rule that is

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determined to be "economically significant" as defined under Executive Order 12866 and concerns an environmental health or safety risk that EPA has reason to believe may have a disproportionate effect on children, the Agency must evaluate the environmental health or safety effects of the planned rule on children and explain why the planned regulation is preferable to other potentially effective and reasonably feasible alternatives considered by the Agency. This proposed rule is not subject to the Executive order because it is not economically significant as defined in Executive Order 12866 and because the Agency does not have reason to believe that the environmental health or safety risks addressed by this action present disproportionate risks to children. The Agency has determined that the PVCP-PIPs that would be exempted by this rule pose only a low probability of risk to human health, including the health of infants and children, and that there is a reasonable certainty no harm will result to infants and children from aggregate exposure to residues of these PVCP-PIPs in food. Existing information suggests there are no disproportionate effects on infants or children from dietary or other exposures. EPA's assessment and the results of its assessment are contained in Unit VIII. of the companion document published elsewhere in this issue of the **Federal Register** exempting from the FFDCA section 408 requirement of a tolerance, residues of the plant virus coat protein portion of a PVCP-PIP.

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*H. Executive Order 13211: Actions that Significantly Affect Energy Supply, Distribution, or Use*

This rule is not a "significant energy action" as defined in Executive Order 13211, *Actions Concerning Regulations that Affect Energy Supply, Distribution, or Use* (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. Further, we have concluded that this rule is not likely to have any adverse energy effects. EPA's proposal would exempt certain PVCP-PIPs from existing FIFRA requirements. PVCP-PIPs are typically used as food or feed, and thus, a rule that reduces regulatory requirements would not be anticipated to have any impact on energy supply, distribution, or use. Moreover, given that the proposal would reduce the regulatory burden by exempting such products from existing regulatory requirements, EPA anticipates that any impact the rule might have on energy supplies (if, for example, such products are used for ethanol) would be purely beneficial.

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*I. National Technology Transfer Advancement Act*

This rule does not involve a regulatory action that would require the Agency to consider voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104-113, section 12(d) (15 U.S.C. 272 note). Section 12(d) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or otherwise impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, business practices, etc.) that are developed or adopted by voluntary consensus standards bodies. The NTTAA requires EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards when the NTTAA directs the Agency to do so.

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

Pursuant to Executive Order 12898, *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994), EPA has considered environmental justice related issues with regard to the potential impacts of this action on the environmental and health conditions in low-income and minority communities. The Agency is required to consider the potential for differential impacts on sensitive sub-populations. EPA considered available information on the sensitivities of subgroups as pertains to the exemptions. EPA concluded that no subgroup would be differentially affected. See also the companion document "Exemption from the Requirement of a Tolerance under the Federal Food, Drug, and Cosmetic Act for Residues of Plant Virus Coat Proteins that are Part of a Plant-Incorporated Protectant (PVC-Proteins)" published elsewhere in this issue of the **Federal Register**.

**XI. Scientific Advisory Panel, USDA, and Congressional Review**

In accordance with FIFRA section 25(d), EPA submitted this proposed rule to the FIFRA Scientific Advisory Panel on September 20, 2006 for comment as to the impact on health and the environment of the action proposed. A copy of the proposed rule was forwarded to the Secretary of Agriculture on October 2, 2006. Copies of the proposed rule were also forwarded to the Committee of Agriculture of the House of Representatives and the Committee on Agriculture, Nutrition, and Forestry of the Senate on October 2, 2006.

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Under 5 U.S.C. 801(a)(1)(A), as added by the Small Business Regulatory Enforcement Fairness Act of 1996, EPA submitted a report containing this proposed rule and other required information on [INSERT DATE] to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication in this issue of the Federal Register. This rule is not a "major rule" as defined by 5 U.S.C. 804(2).¶

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**List of Subjects in 40 CFR Part 174**

Environmental protection, Administrative practice and procedures, Pesticides and pests,

Dated:_____

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*Administrator*.

Therefore, it is proposed that 40 CFR chapter I be amended as follows:

**PART 174 –[AMENDED]**

1. The authority citation for part 174 would continue to read as follows:

**Authority:** 7 U.S.C. 136-136y and 21 U.S.C. 346a and 371.

2. By alphabetically adding to § 174.3 new definitions to read as follows:

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**§ 174.3 Definitions.**

* * * * *

*Naturally infect* means to infect by transmission to a plant through direct plant-to-plant contact (e.g., pollen or seed), an inanimate object (e.g., farm machinery), or vector (e.g., arthropod, nematode, or fungus). It does not include infection by transmission that occurs only through intentional human intervention, e.g., manual infection in a laboratory or greenhouse setting.

* * * * *

*PVCP-PIP* is a plant-incorporated protectant derived from one or more genes that encode a coat protein of a virus that naturally infects plants. This includes plant-incorporated protectants derived from one or more plant viral coat protein genes that produce only RNA and no virus-related protein.

*PVC-protein* is the plant virus coat protein portion of a PVCP-PIP.

* * * * *

*United States* means a State, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, the Trust Territory of the Pacific Islands, and American Samoa.

*Unmodified* means having or coding for an amino acid sequence that is identical to an entire coat protein of a naturally occurring plant virus.

* * * * *

*Virtually unmodified* means having or coding for an amino acid sequence that is identical to an entire coat protein of a naturally occurring plant virus, except for the addition of one or two amino acids at the N- and/or C-terminus other than cysteine, asparagines, serine, and threonine and/or the deletion of one or two amino acids at the N- and/or C-terminus.

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*Weedy species* means a species that is an aggressive competitor in natural ecosystems.

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3. In §174.21 by revising the introductory text and paragraph (c) to read as follows:

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**§ 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 all of the following criteria. Plant-incorporated protectants that are not exempt from the requirements of FIFRA under this subpart are subject to all the requirements of FIFRA.

*  *  *  *  *

(c) Any inert ingredient that is part of the plant-incorporated protectant is on the list codified at §§ 174.485 through 174.486.

4. By adding § 174.27 to subpart B to read as follows:

**§ 174.27_____ Plant-incorporated protectant derived from a coat protein gene(s) from a virus(es) that naturally infects plants (PVCP-PIP).**

In order for a plant-incorporated protectant derived from one or more genes that encode a coat protein of a virus that naturally infects plants (PVCP-PIP) to be exempt, the criteria in paragraphs (a), (b), and (c) and the requirements in paragraph (d) of this section must all be satisfied.

(a) The criterion in paragraph (a) of this section is satisfied if either paragraph (a)(1) or paragraph (a)(2) of this section applies:

(1) The plant containing the PIP is one of the following: anthurium (*Anthurium* spp.), asparagus (*Asparagus officinale*), avocado (*Persea americana*), banana (*Musa acuminata*), barley (*Hordeum vulgare*), bean (*Phaseolus vulgaris*), cacao (*Theobroma cacao*), carnation (*Dianthus caryophyllus*), chickpea (*Cicer arietinum*), citrus (*Citrus* spp., e.g., *Citrus aurantifolia, Citrus limon, Citrus paradisii, Citrus sinensis*), coffee (*Coffea arabica* and *Coffea canephora*), corn (*Zea maize*), cowpea (*Vigna unguiculata*), cucumber (*Cucumis sativus*), gerbera (*Gerbera* spp.), gladiolus (*Gladiolus* spp.), lentil (*Lens culinaris*), mango (*Mangifera indica*), orchids (Orchidaceae), papaya (*Carica papaya*), pea (*Pisum sativum*), peanut (*Arachis hypogaea*), pineapple (*Ananas comosus*), potato (*Solanum tuberosum*), soybean (*Glycine max*), starfruit (*Averrhoa carambola*), sugarcane (*Saccharum officinarum*), or tulips (*Tulipa* spp.).

(2) The Agency determines after review that the plant containing the PIP meets paragraphs (a)(2)(i), (a)(2)(ii), and (a)(2)(iii) of this section:

(i) Has no wild or weedy relatives in the United States with which it can form viable hybrids in nature, and

(ii) Is not a weedy or invasive species outside of agricultural fields in the United States, and

(iii) Is unlikely to establish weedy or invasive populations outside of agricultural fields in the United States even if the plant contains a PVCP-PIP.

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(b) The criterion in paragraph (b)of this section is satisfied if either paragraph (b)(1)(i), paragraph (b)(1)(ii), or paragraph (b)(2) of this section applies:

(1)(i) The viral pathotype used to create the PVCP-PIP has naturally infected plants in the United States and naturally infects plants of the same species as those containing the PVCP-PIP, or

(ii) The genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant.

(2) The Agency determines after review that viruses that naturally infect the plant containing the PVCP-PIP are unlikely to acquire the coat protein sequence through recombination and produce a viable virus with significantly different properties than either parent virus.

(c) The criterion in paragraph (c) of this section is satisfied if either paragraph (c)(1) or paragraph (c)(2) of this section applies:

(1) The genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance:

(i) Is inserted only in an inverted repeat orientation or lacking an initiation codon for protein synthesis such that no PVC-protein is produced in the plant, or

(ii) Encodes only a single virtually unmodified viral coat protein. Multiple PVC-proteins could each separately meet this criterion. Chimeric PVC-proteins do not qualify.

(2) The Agency determines after review that the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance:

(i) Encodes a protein that is minimally modified from a coat protein from a virus that naturally infects plants, or

(ii) Produces no protein.

(d)(1) Records to support exemption determinations made by the developer of a PVCP-PIP under paragraphs (a)(1), (b)(1), or (c)(1) of this section; to support a submission of information under paragraphs (a)(2), (b)(2), or (c)(2) of this section; or to support a certification made by the developer that a PVCP-PIP meets § 174.21(b) and/or § 174.21(c) must be maintained by the developer of the product for the duration of time that the PVCP-PIP is sold or distributed. Such records must be made available for inspection and copying, or otherwise submitted to the Agency for review upon request by EPA or its duly authorized representative.

(2) Information adequate to support claims for an Agency-determined exemption must be submitted for review to the Office of Pesticide Programs, Attention: PVCP-PIP Exemption.

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(3) A statement notifying the Agency and certifying the accuracy of any determination made by the developer that a PVCP-PIP meets § 174.21(b), § 174.21(c), paragraph (a)(1) of this section, paragraph (b)(1) of this section, and/or paragraph (c)(1) of this section must be signed by the developer and submitted to the Office of Pesticide Programs, Attention: PVCP-PIP Exemption. Any such statement must be submitted at the time of a first submission, if any, of information under paragraph (d)(2) of this section for a particular PVCP-PIP. If a PVCP-PIP satisfies paragraphs (a)(1), (b)(1), and (c)(1)) of this section and §§ 174.21(b) and (c), the developer must submit a notification to the Agency of that determination and certify that the PVCP-PIP qualifies for exemption under FIFRA, i.e., that the PVCP-PIP meets §§ 174.21(a), (b), and (c). This certification must contain:

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(i) The name of the crop (including genus and species) containing the PVCP-PIP.

(ii) The name of the virus from which the coat protein gene was derived.

(iii) The name of the virus(es) to which resistance is conferred.

(iv) When available, a unique identifier.

5. By revising §174.480 to read as follows:

**§ 174.480 Scope and purpose.**

This subpart lists the inert ingredients that may be used in a plant-incorporated protectant listed in subpart B of this part and whose residues are either exempted from the requirement of a tolerance under FFDCA or no tolerance would otherwise be required.

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6. By adding § 174.486 to read as follows:

**§ 174.486 Inert ingredients that may be used with PIPs in certain plants.**

The following must be used in a plant that satisfies § 174.27(a) in order to be exempt from the requirements of FIFRA.

(a) *Beta*-D-glucuronidase (GUS) from *Escherichia coli* and the genetic material necessary for its production.

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(b) Neomycin phosphotransferase II (NPTII) and the genetic material necessary for its production.

(c) Phosphomannose isomerase (PMI) and the genetic material necessary for its production.

(d) CP4 enolpyruvylshikimate-3-phosphate (CP4 EPSPS) and the genetic material necessary for its production.

(e) Glyphosate oxidoreductase (GOX or GOXv247) and the genetic material necessary for its production.

(f) Phosphinothricin acetyltransferase (PAT) and the genetic material necessary for its production.

(g) Partial tetracycline resistance gene under the control of a bacterial promoter as present in papaya line 55-1.

[FR Doc. 06–XXXXX Filed XX–XX–06; 8:45 am]
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