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.

(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:

(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.

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.

(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.

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[EPA–HQ–OPP–2006–0643; FRL–8100–5]

RIN 2070–AD49

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); Supplemental Proposal

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is proposing to exempt from the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408 requirement of a tolerance, residues of coat proteins from viruses that naturally infect plants that humans consume when such coat proteins are produced in living plants as part of a plant-incorporated protectant (PIP) and the criteria proposed for this exemption are met. EPA believes there is a reasonable certainty that no harm will result from aggregate exposure to such residues, including all anticipated dietary exposures and all other exposures for which there is reliable information. This proposed exemption would eliminate the need to establish a maximum permissible level in food for these residues.

DATES: Comments must be received on or before July 17, 2007.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPP–2006–0643, by one of the following methods:

- *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 Bldg.), 2777 S. Crystal Dr., 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 Facility telephone number is (703) 305–5805.
- *Instructions*: Direct your comments to docket ID number EPA–HQ–OPP–

2006–0643. 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 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.

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 Bldg.), 2777 S. Crystal Dr., 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 Facility 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*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Document 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 PIPs. 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.
- Food manufacturing (NAICS code 311), e.g., establishments primarily engaged in the manufacturing of food or feed.
- 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., establishments 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 or not 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 applicable provisions of 40 CFR part 174. If you have questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

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

1. *Docket*. EPA has established a docket for this action under docket ID number EPA–HQ–OPP–2006–0643. 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 Bldg.), 2777 S. Crystal Dr., 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 Facility telephone number is (703) 305–5805.

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. What Action is the Agency Proposing?

EPA is proposing to exempt the following from the FFDCA section 408 requirement of a tolerance: Residues of coat proteins from viruses that naturally infect plants that humans consume as part of a normal diet, including any metabolites or degradates of those coat proteins, when such coat proteins are produced in living plants as part of a PIP and the criteria proposed for this exemption are met. The proposed criteria are intended to clearly identify and exempt only those residues for which a long history of safe exposure and consumption can support exemption. EPA believes there is a reasonable certainty that no harm will result from aggregate exposure to such residues, including all anticipated dietary exposures and all other exposures for which there is reliable information. This proposed exemption would eliminate the need to establish a maximum permissible level in food for these residues.

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

EPA is proposing to establish this tolerance exemption on its own initiative under sections 408(e) and (c) of FFDCA, 21 U.S.C. 346a(c) and (e). Under FFDCA section 408, EPA regulates pesticide chemical residues by establishing tolerances limiting the amounts of residues that may be present in or on food or by establishing exemptions from the requirement of a tolerance for such residues. Food includes articles used for food or drink by humans or animals. A food containing pesticide residues may not be moved in interstate commerce without an appropriate tolerance or an exemption from the requirement of a tolerance.

Section 408 of FFDCA applies to all ''pesticide chemical residues,'' which are defined as residues of either a ''pesticide chemical'' or ''any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical'' (21 U.S.C. 321(q)(2)). FFDCA defines ''pesticide chemical'' as: ''any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide'' (21 U.S.C. 321(q)(1)). The Federal Insecticide, Fungicide, and Rodenticide Act (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)).

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the exemption is ''safe.'' Section 408(c)(2)(A)(ii) of FFDCA defines ''safe'' to mean 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.'' This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Pursuant to section 408(c)(2)(B) of FFDCA, in establishing or maintaining in effect an exemption from the requirement of a tolerance, EPA must take into account the factors set forth in section 408(b)(2)(C) of FFDCA, which require EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to ''ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue. . . .'' Additionally, section 408(b)(2)(D) of FFDCA requires that the Agency consider ''available information concerning the cumulative effects of a particular pesticide's residues'' and ''other substances that have a common mechanism of toxicity.''

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. First, EPA determines the toxicity of pesticides. Second, EPA examines exposure to the pesticide through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings.

Section 408(e)(1)(C) of FFDCA also grants EPA the authority to establish ''general procedures and requirements to implement this section'' (21 U.S.C. 346a(e)(1)(C)).

IV. Context

A. What is the Relationship of this Proposal to Other Regulatory Requirements under FIFRA and FFDCA?

When the genetic material that encodes an entire or a portion of a plant virus coat protein is introduced into living plants with the intention of preventing or mitigating viral disease in the plants, the genetic material and any substances produced from the genetic material constitute a type of pesticide termed a ''plant virus coat protein plant-incorporated protectant'' or ''PVCP-PIP.'' PVCP-PIPs 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)). PVCP-PIPs are considered pesticide chemicals under FFDCA which defines a ''pesticide chemical'' as ''any substance that is a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act, including all active and inert ingredients of such pesticide.'' As such, residues of PVCP-PIPs in or on food (hereinafter simply ''in food'') are subject to FFDCA section 408.

Since PVCP-PIPs are a relatively newly described type of pesticide, the discussion in this unit provides information explaining how this FFDCA proposed action on residues of the plant virus coat protein portion of a PVCP-PIP (called here the ''PVC-protein'') would affect the FFDCA and FIFRA status of the complete PVCP-PIP. To this end, several pieces of information are presented: A description of the anticipated residues of PVCP-PIPs; a discussion of the FFDCA status, either current or proposed, of all anticipated PVCP-PIP residues; a discussion of what would be considered in determining the FFDCA status of the complete PVCP-PIP; and a discussion of how the FFDCA status of PVCP-PIP residues relates to the FIFRA status of the PVCP-PIP.

1. *What are the components of a PIP*? A PIP is defined at 40 CFR 174.3 as ''a pesticidal substance that is intended to be produced and used in a living plant, or in the produce thereof, and the genetic material necessary for production of such a pesticidal substance. It also includes any inert ingredient contained in the plant, or produce thereof.''

2. *What are the anticipated residues of PVCP-PIPs*? Based on the definition of a PIP, EPA anticipates residues of a PVCP-PIP would include residues of any PVC-protein; the nucleic acids associated with the PVCP-PIP, e.g., the genetic material encoding the PVC-protein; and any inert ingredient as defined for PIPs at 40 CFR 174.3. Each of these three classes of residues will also include any metabolite and degradate of that class in accordance with FFDCA section 201 that defines a ''pesticide chemical residue'' as ''a residue in or on raw agricultural commodity or processed food of (A) a pesticide chemical; or (B) any other added substance that is present on or in the commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical'' (21 U.S.C. 321(q)(2)).

3. *What is the FFDCA status of each identified class of residues*? For the complete PVCP-PIP to be exempt from FFDCA section 408, all three classes of PVCP-PIP residues listed above must be exempt, i.e., residues of the PVC-protein, the nucleic acids associated with the PVCP-PIP, and any inert ingredient as defined for PIPs at 40 CFR 174.3. The units below discuss the status of residues of the PVC-protein under this proposed action, the status of residues of the nucleic acids associated

with the PVCP-PIP, and the status of residues of inert ingredients.

i. *Residues of PVC-proteins*. Residues in this category consist of residues of the PVC-protein and any metabolites or degradates of that protein. This proposal would exempt from tolerance requirements residues of PVC-proteins that meet certain criteria.

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 viral replication, movement within the plant, and transmission of the virus from plant to plant by insects (Ref. 1). Current scientific information suggests that prevention or mitigation of disease by some PVCP-PIPs may be protein-mediated because for certain PVCP-PIPs efficacy is correlated with the concentration of coat protein produced by the transgene (Ref. 2). In protein-mediated resistance, the coat protein is thought to impede the infection cycle by interfering with the disassembly of infecting viruses (Ref. 3). In such cases, EPA would consider the PVC-protein to be the pesticidal substance. Residues of such PVC-proteins and their metabolites and degradates that meet the proposed criteria would be covered by this proposal.

In transgenic plants employing a second mechanism of resistance called post-transcriptional gene silencing (PTGS), prevention or mitigation of viral disease is not correlated with the level of PVC-protein expression. Indeed, virus resistance can occur even when a coat protein gene expresses untranslatable RNA sequences and no PVC-protein is detected. In PTGS, RNA fragments appear to be pesticidal substances (Ref. 3). (See Unit II.E. of the companion document published elsewhere in this **Federal Register** for a more detailed description of PTGS.) Even when PTGS is the mechanism of resistance, any PVC-protein that might be produced is part of the PVCP-PIP. Residues of such PVC-proteins and their metabolites and degradates that meet the proposed criteria are also covered by this proposal.

ii. *Residues of nucleic acids*. Residues in this category include residues of the genetic material necessary for the production of the pesticidal substance and the genetic material for any inert ingredient as defined at 40 CFR 174.3. Residues in this category would also include residues of any nucleic acids effecting the pesticidal action of the PVCP-PIP, e.g., residues of nucleic acids involved in PTGS.

''Nucleic acids'' are defined at 40 CFR 174.3 as ''ribosides or deoxyribosides of adenine, thymine, guanine, cytosine, and uracil; polymers of the deoxyribose-5'-monophosphates of thymine, cytosine, guanine, and adenine linked by successive 3'-5' phosphodiester bonds (also known as deoxyribonucleic acid); and polymers of the ribose-5'-monophosphates of uracil, cytosine, guanine, and adenine linked by successive 3'-5' phosphodiester bonds (also known as ribonucleic acid). The term does not apply to nucleic acid analogues (e.g., dideoxycytidine), or polymers containing nucleic acid analogues.'' Nucleic acids are currently exempt from FFDCA tolerance requirements. See 40 CFR 174.475 and 66 FR 37817 (July 19, 2001) (FRL–6057–5). EPA is not proposing to amend this exemption.

iii. *Residues of any inert ingredient*. Residues in this category consist of residues of any inert ingredient that is part of a PVCP-PIP and any metabolite or degradate of an inert ingredient. An inert ingredient for a PIP is defined at 40 CFR 174.3 as ''any substance, such as a selectable marker, other than the active ingredient, where the substance is used to confirm or ensure the presence of the active ingredient, and includes the genetic material necessary for the production of the substance, provided that genetic material is intentionally introduced into a living plant in addition to the active ingredient.''

A tolerance or tolerance exemption is required for residues of any substance in food that meets the 40 CFR 174.3 definition of an inert ingredient (e.g., a selectable marker intentionally introduced into the plant as part of a PVCP-PIP such as a protein conferring resistance to an herbicide). Part 180 and part 174, subpart W, of 40 CFR list inert ingredients for which tolerance exemptions have been established. If an inert ingredient is not listed at part 180 or part 174, subpart W, an applicant would need to petition the Agency in accordance with 40 CFR 180.7 to obtain a tolerance or tolerance exemption for residues of that particular inert ingredient in order for food containing residues of the PVCP-PIP to move in interstate commerce—even if all other residues of the PIP are exempt.

4. *What is the relationship between the FIFRA status of a PVCP-PIP and the FFDCA status of its residues*? A tolerance exemption does not exempt a PVCP-PIP from FIFRA regulation. However, in order for a PVCP-PIP in food plants to be exempted from FIFRA regulation, a tolerance exemption must exist for all residues associated with a PVCP-PIP or FFDCA requirements must be otherwise met. (See the general qualification for exemption under FIFRA at 40 CFR 174.21(b).) The FIFRA status of a PVCP-PIP is determined based on factors in addition to FFDCA section 408 considerations because FIFRA requires the Agency to consider additional risk and benefit issues beyond those addressed under section 408 of FFDCA. Concurrently with this proposed FFDCA exemption, the Agency is publishing a proposal under which PVCP-PIPs might meet the general qualification for FIFRA exemption at 40 CFR 174.21(a) based on different criteria than the criteria in this proposal.

B. 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, NY; on September 8–9, 1988, a ''Transgenic Plant Conference'' in Annapolis, MD; on November 6–7, 1990, a conference on ''Pesticidal Transgenic Plants: Product Development, Risk Assessment, and Data Needs'' in Annapolis, MD; on April 18–19, 1994, a ''Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops'' in Annapolis, MD; 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, NC. Information from these conferences has been incorporated as appropriate in development of this proposed rule.

EPA has requested the advice of two scientific advisory groups at five meetings while developing its approach to PIPs. On December 18, 1992, EPA convened the 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 the SAP on October 13–14, 2004. On December 6–8, 2005, EPA requested the SAP to respond to a series of scientific

questions related to this proposal. EPA carefully considered advice from all five meetings in the development of this proposed rule.

2. **Federal Register** *documents*. The history of this proposal consists of the original proposed exemption that appeared in the November 23, 1994 **Federal Register** (59 FR 60545) (FRL–4755–4), a supplemental document that appeared in the May 16, 1997 **Federal Register** (62 FR 27149) (FRL–5716–6), and a supplemental document which appeared in the July 19, 2001**Federal Register** (66 FR 37855) (FRL–6760–4).

i. *November 23, 1994*. EPA published a package of five separate documents in the November 23, 1994 **Federal Register** which described EPA's policy and proposals for PIPs under FIFRA and FFDCA (59 FR 60496, 60519, 60535, 60542, and 60545). In one of these documents (59 FR 60545), EPA proposed to exempt from the 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 as follows:

''Residues of coat proteins from plant viruses, or segments of the coat 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) to provide the public with an opportunity to comment on EPA's analysis of how certain FQPA amendments to FFDCA and FIFRA apply to the proposed exemption from the requirement of a tolerance for residues of PVC-proteins.

In that 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 FQPA, EPA did take into account most of the same factors in issuing its 1994 proposal to exempt residues of PVC-proteins, or 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:

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,

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,

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

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, if not the only, route of exposure will be dietary, and

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.

iii. *July 19, 2001*. In July of 2001, EPA published a supplemental document in the **Federal Register** (66 FR 37855) to provide 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 PVCP-PIPs contained in the NRC report entitled ''Genetically Modified Pest-Protected Plants: Science and Regulation'' (Ref. 4). In addition, the public was given an opportunity to comment on a clarification of the language in the original 1994 proposal on PVCP-PIPs that EPA was considering in response to public comment. The purpose of the clarification was to circumscribe more clearly those residues proposed for exemption.

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

This 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 this proposal should submit them (or relevant portions) again during this comment period.

C. Rationale Supporting the Proposed FFDCA Tolerance Exemption

EPA's base of experience with viruses infecting food plants has led the Agency to draw three conclusions on which it is relying to support this proposed tolerance exemption for residues of PVC-proteins in food. 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. These conclusions are derived from a base of experience and information sufficient to support this proposed tolerance exemption.

1. *Always been part of food supply without adverse effects*. Virus-infected food plants have always been a part of the human and domestic animal food supply (Refs. 5, 6, 7, 8, 9, and 10). Most plants are infected by at least one virus, and components of plant viruses, including coat proteins, are often found in the produce of crop plants. For example, at the beginning of this century virtually every commercial cultivar of potatoes grown in the United States and Europe was infected with either one or a complex of potato viruses (Ref. 10). Even plants that show no disease symptoms are often found to be infected with viruses (Refs. 9 and 11). In addition, a common agricultural practice used since the 1920s for protection against viral disease involves intentionally inoculating healthy plants with a mild form of a virus in order to prevent infection by a more virulent form (Ref. 11). A recent analysis of viral sequences isolated from fecal samples of healthy humans showed the presence of large quantities of plant pathogenic viruses from 35 different plant virus species with evidence suggesting dietary origins for the most prevalent (Ref. 12). A great deal of information supports the ubiquitous appearance of plant viruses in foods, and to date there have been no reports of adverse human or animal health effects associated with consumption of plant viruses in food.

The National Research Council (NRC) observed in its 2000 report that ''[h]uman or animal consumption of plants with viral coat proteins is widely considered to be safe, on the basis of common exposure to these types of proteins in nontransgenic types of food'' (Ref. 4). The FIFRA SAP addressed the issue of dietary risk at its December 18, 1992 meeting (Ref. 13). The SAP stated, ''Since viruses are ubiquitous in the agricultural environment at levels higher than will be present in transgenic

plants, and there has been a long history of 'contamination' of the food supply by virus coat protein, there is scientific rationale for exempting transgenic plants expressing virus coat protein from the requirement of a tolerance.'' The FIFRA SAP again discussed PVC-proteins on October 11–13, 2004, and ''agreed that (because of the human history of consuming virus infected food), unaltered PVCPs do not present new dietary exposures'' (Ref. 14). The 2005 SAP also agreed that ''[h]istorically, virus infected plants have been a part of the human and domestic animal food supply without adverse human or animal health effects'' (Ref. 15).

In general, EPA anticipates that dietary exposure through human and animal consumption of plants containing residues of PVC-proteins that would qualify for the proposed exemption will be similar to or less than the dietary exposure to plant virus coat proteins currently found in food plants naturally infected with viruses. Experiments have shown the amount of PVC-protein found in plants containing a PVCP-PIP to be as much as one hundred- to one thousand-fold lower than the amount of plant virus coat protein found naturally in virus-infected plants, even when the resistance is believed to be mediated by the PVC-protein itself (Refs. 8 and 16). The difference in amount of PVC-protein present is even more marked for virus-resistant plants employing resistance mediated by RNA. In such cases, little to no detectable coat protein is produced in a plant containing a PVCP-PIP (Refs. 3 and 17). Such information conforms to information EPA has received from the scientific advisory groups the Agency has consulted (see Unit IV.B.1.). Although the Agency believes that the PVC-proteins which qualify for this proposed tolerance exemption are safe at any level given the long history of human dietary exposure to high levels of such proteins, the anticipated low levels of exposure to PVC-proteins in food lend additional support to this proposed exemption.

2. *Not infectious to humans.* Any virus/host relationship is characterized by a high degree of specificity (Ref. 8). Plant viruses usually infect plants only within a certain taxonomic group and are unable to infect humans or other vertebrates (Refs. 18 and 19). Cellular machinery for processing genetic material is highly specific. For example, plant viruses are unable to recognize and attach to the specific sites on mammalian cells needed to penetrate the cell membrane, and plant viruses cannot be processed by mammalian cellular machinery. Plant viruses therefore do not and cannot infect mammals and other vertebrates. In addition, multiple virus components in addition to the coat protein have a role in and are necessary for plant infection. Plant viral coat proteins alone are not infectious to plants, and whole, intact plant viruses are not infectious to humans. Therefore, it is reasonable to assume that a single component of plant viruses, e.g., the PVC-protein, will not be infectious to humans.

3. *No toxic or allergenic effects to animals or humans.* Humans and domestic animals have been and are exposed to plant viruses in the food supply because most crops are frequently infected with plant viruses. Food from these crops has been and is being consumed with no indication of human or animal toxicity related to plant virus infections. Additionally, in experiments where purified plant virus preparations have been injected into laboratory animals, no adverse effects have been reported (Ref. 17). Furthermore, the Agency is not aware of any coat protein from a virus that naturally infects plants that has been identified as a food allergen for humans. Finally, the amount of PVC-protein likely to be found in food is anticipated to generally be lower than the amount of virus coat protein found in food naturally infected with plant viruses (as discussed in Unit IV.C.1.).The 2005 SAP questioned whether an increased propensity for allergies in humans affects the relevance of the history of safe use to the current safety of virus coat proteins. Several studies have documented a general increase in atopy in human populations; these studies show that over the last several decades there has been an increasing proportion of human populations that have an allergic sensitization to particular allergens (Refs. 20, 21, and 22). However, there is no reason to believe that PVC-proteins in the environment would have any impact on this phenomenon. EPA is aware of no evidence that previously nonallergenic substances are now able to elicit an immune response, and no plant virus coat proteins have ever been identified as allergens. Moreover, the amount of plant virus coat protein in the environment is not expected to increase due to the use of PVCP-PIPs. On the contrary, PVCP-PIPs generally express PVC-protein at levels below that found in natural virus infections, and the virus-resistant phenotype conferred by PVCP-PIPs should significantly reduce levels of natural virus infection in plants, thereby decreasing the amount of plant virus coat protein in the environment where PVCP-PIPs are deployed.

D. Key Issue: Determination of Natural Virus Variation

A key issue facing EPA in developing this exemption is how to clearly describe for regulatory purposes those PVC-proteins that are within the range of naturally occurring plant virus coat proteins and to which the rationale discussed in Unit IV.C. therefore applies. If a plant virus coat protein gene is isolated in nature and not modified, the PVC-protein would clearly be within the range of natural variation. However, many coat protein genes are modified in creating a PVCP-PIP, e.g., to increase product efficacy or allow appropriate expression in the plant. Some of these modifications may affect a PVC-protein, although most of these variations would not be expected to differ significantly (e.g., in terms of toxicity or allergenicity) from the naturally occurring coat protein. In fact, given the considerable variation in naturally occurring viral coat proteins, it is also possible that naturally occurring plant viruses exist with some of the minor modifications that could conceivably be introduced into PVC-proteins.

However, EPA's task of defining this variation is complicated by the variable nature of plant virus genomes and the fact that the full extent of variation for even a single plant virus is currently unknown. Sequencing of plant virus genomes has revealed that a large number of variants exist within most populations of both RNA and DNA viruses. Due to this inherent heterogeneity in virus populations, they are often described as ''quasispecies'' that exist as a pool of different sequences varying around a consensus sequence (Refs. 23, 24, and 25).

Genetic variation in virus populations arises due to several processes including mutation, recombination, and reassortment. Mutation is a change in the genetic material that most commonly occurs when replication errors lead to incorporation of an incorrect nucleotide into the daughter sequence (Ref. 26). New virus variants are also generated by recombination, the natural process that occurs during replication of DNA or RNA whereby new combinations of genes are produced. Recombination is more likely to occur the more closely related viruses are, but recombination between different viral species is also believed to occur (Refs. 27 and 28). Evidence of past recombination having led to the creation of new DNA and RNA viruses has been

found in a number of different groups including bromoviruses (Ref. 29), caulimoviruses (Ref. 30), luteoviruses (Ref. 31), nepoviruses (Ref. 32), cucumoviruses (Ref. 33), and geminiviruses (Refs. 27 and 34). Sequence analysis of viruses from the family Luteoviridae indicated that this family has evolved via both intra- and inter-familial recombination (Ref. 35). In viruses with segmented genomes, variation may also be caused by reassortment whereby entire segments are exchanged between viruses (Ref. 36).

Attempts to describe the range of variation for naturally occurring plant virus coat proteins are complicated not only by variation within species but also by variation among species (See Ref. 37 for review). For example, cucumber mosaic cucumovirus (CMV) has a relatively high degree of variation (Ref. 38) compared to tobacco mild green mosaic tobamovirus (Ref. 39). The greater variability in CMV would be expected based on the relatively wide host range and relatively high recombination rate of this virus. Such wide-ranging, inherent variability confounds attempts to establish meaningful estimates of normal variability for coat proteins of plant viruses as a group.

A large number of viral coat protein sequences are currently available in the literature and in public sequence repositories, e.g., the National Center for Biotechnology Information. However, EPA has concluded that no single standard could capture the degree of variation across all viruses, and hundreds of plant viruses have been identified to date (Ref. 40). It would be at best impractical for EPA to describe individually for all virus groups all potential modifications that would produce a PVC-protein that falls within the range of natural variation given the vast (and yet still incomplete) amount of data that currently exists. The 2005 SAP concurred with these conclusions: ''Currently, it is extremely difficult to identify modifications that would be expected to be 'within the range of natural variation for all virus families'. This would require prior knowledge of the natural variation limits of the individual PVC proteins, which is not available. Specific modifications can be identified that would raise potential concerns, but it is not clear that it is possible to create a comprehensive list of these changes for all virus families'' (Ref. 15).

At the present time, insufficient information exists to develop a standard that would describe *a priori* the degree to which a PVC-protein could be modified and yet still remain within the natural variability of plant virus coat proteins found in virus populations either generally or for any species in particular. In light of this, and relying extensively on the advice of the 2005 FIFRA SAP meeting (Ref. 15), EPA has developed two proposals to exempt PVC-protein residues from the requirement of a tolerance:

1. A categorical exemption for a subset of PVC-proteins based on developer self-determination that the encoded PVC-protein is virtually unmodified when compared to an entire unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part, and

2. An exemption for more extensively modified proteins that is conditional on an Agency determination after review that the encoded PVC-protein is minimally modified when compared to an unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part.

E. Structure of the Proposed FFDCA Tolerance Exemption

1. *Proposed categorical exemption.* Under the proposed exemption at § 174.477(a), when the encoded PVC-protein is virtually unmodified when compared to an entire unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part, the residues of the PVC-protein would be exempt from the requirement of a tolerance without Agency review. If the PVC-protein is expressed from a plant virus coat protein gene that was isolated from a virus found naturally in a food plant in the United States and was not modified, the PVC-protein would meet this criterion. Additionally, a PVC-protein would meet this criterion if the developer has evidence showing it has an amino acid sequence that is virtually unmodified when compared to an unmodified plant virus coat protein sequence from a virus that naturally infects plants that humans consume, e.g., as found in a database. Although EPA cannot *a priori* identify all existing natural coat protein variants, the requirement of being virtually unmodified when compared to an entire unmodified coat protein ensures that the exempted PVC-protein falls within the existing base of experience on which the proposed exemption relies.

EPA intends, with the requirement that the PVC-protein be virtually unmodified when compared to ''an entire unmodified coat protein,'' to exclude from the categorical exemption residues of modified PVC-proteins, e.g., PVC-proteins containing insertions, deletions, or amino acid substitutions (except as described below by the definition of virtually unmodified), as well as chimeric PVC-proteins that are encoded by a sequence constructed by fusing portions of two or more plant virus coat protein genes. EPA is proposing to exclude such PVC-proteins from the categorical exemption because of advice from the 2005 SAP that insufficient information exists at this time to allow EPA to describe *a priori* a single standard articulating which of these types of changes would be consistently expected to fall within the natural range of variation of viruses and/or which types of changes could be determined not to affect toxicity or allergenicity without any EPA review (see Unit IV.D.).

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 is considering several options for defining the term virtually unmodified. Under this proposal, any virtually unmodified PVC-protein would qualify for a tolerance exemption without Agency review. Under one option, this term would 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.'' As noted by the 2005 SAP, the terminal ends of a protein ''are the least structurally constrained regions of a protein. As such, the ends can be thought of as being essentially 'unstructured,' and therefore unlikely to serve as allergenic epitopes or to make major contributions to the overall structure of the molecule. Addition (or deletion) of one or two amino acids is unlikely to change this.'' However, the SAP also noted the possibility that the addition of amino acids such as cysteine with side chains that could promote cross-linking or aggregation between molecules or other amino acids that can serve as sites for post-translational modifications should be evaluated on a case-by-case basis (Ref. 15). EPA has identified cysteine, asparagine, serine, and threonine as the amino acids containing side chains that could promote cross-linking or serve as sites for post-translational modifications. EPA therefore excludes the addition of these amino acids from the proposed definition of virtually unmodified. The 2005 SAP report mentioned alanine as an amino acid involved in

glycosylation; however, EPA has found no evidence that alanine is involved in glycosylation or promotes cross-linking. The Agency has therefore not excluded the addition of alanine under the definition of virtually unmodified.

The Agency is also considering two possible changes to the above definition of virtually unmodified. The first change would remove the restriction that cysteine, asparagine, serine, or threonine may not be added to the naturally occurring protein. Under this alternative, a PVC-protein would qualify for the tolerance exemption without Agency review if it has an amino acid sequence that is identical to an entire coat protein of a naturally occurring plant virus except for the addition, substitution, or deletion of one or two amino acids at the N- and/or C-terminus. The rationale underlying such an alternative would be that addition of any amino acid to the N- or C-terminus, e.g., including those that could be glycosylated, is unlikely to introduce any concern. In order for an amino acid to be glycosylated, a protein must also have a specific enzyme recognition site. The creation of such a recognition site by the addition, substitution, or deletion of one or two amino acids, particularly at the end of the protein, is expected to be extremely rare because it would involve randomly producing a set of amino acids involved in a specific interaction. The addition of an amino acid with a side group that is capable of forming a covalent bond, e.g., cysteine, is likewise unlikely to alter the safety of the expressed protein. Such amino acid residues would typically be unavailable due to interactions that occur within the protein's normal folding conformation. A plant virus coat protein is large enough that protein functionality or chemistry would not be dramatically different from a PVC-protein that is identical except for its possessing two additional amino acids at the N- and/or C-terminus. As previously stated, the 2005 SAP said the terminal ends of a protein ''are the least structurally constrained regions of a protein'' (Ref. 15). In addition, virus coat proteins are self-assembling, structural proteins that contain elements necessary for continual infection and replication of the entire virus particle. As a structural element of a virus particle, one important function of the coat protein is the ability to interact with itself to form stable particles. Most if not all plant virus coat proteins will naturally aggregate (Refs. 41 and 42), so the addition of amino acids that could promote cross-linking or aggregation would not fundamentally change the nature of the PVC-protein.

The second change to the above definition of *virtually unmodified* that the Agency is considering would allow truncated proteins to fall under the definition. Under this alternative, a PVC-protein would be exempt without Agency review if it has an amino acid sequence that is identical to *a single contiguous portion* of a coat protein of a naturally occurring plant virus, except for the addition or substitution of one or two amino acids at the N- and/or C-terminus of the single contiguous portion other than cysteine, asparagine, serine, and threonine. EPA intends that ''identical to a single contiguous portion'' would exclude proteins with internal modifications. The rationale underlying such an alternative would be that truncated PVC proteins have been reported to occur in nature (Ref. 43), as pointed out by the 2005 SAP. ''Naturally occurring truncated forms of the PVCs could be generated by post-transcriptional and translational events, including incomplete translation due to routine errors causing a ribosome to dissociate from an mRNA, post-translational processing, the presence of a mutation that introduces a premature stop codon, or by infrequent translation initiation at downstream AUGs. . . . Whether the truncation is at the N- or C-terminus is not relevant to allergenicity or toxicity'' (Ref. 15). The SAP also said, ''Determining 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. If a truncated PVC-protein does fall within the range of natural variation, the likelihood of increased toxicity and allergenicity would be low'' (Ref. 15). However, such a database may not be necessary because the potential for toxicity and allergenicity of a whole plant virus coat protein is low enough that the likelihood of a truncated form of such a protein being toxic or allergenic would not rise to the level requiring regulation. Such a change in toxicity or allergenicity would require the truncation to expose new allergenic epitopes or specific recognition/binding sites in the protein that could make the protein toxic, but there is no indication that plant virus coat proteins possess such regions. The 2000 SAP indicated that ''[i]n general, peptide fragments that result from the breakdown of proteins are less toxic than the intact protein'' (Ref. 44).

Either of the changes discussed above could be adopted alone, or both could be adopted together. If EPA adopts both changes, a PVC-protein would be exempt from the requirement of a tolerance without Agency review if it has an amino acid sequence that is identical to *a single contiguous portion* of a coat protein of a naturally occurring plant virus; except for the addition or substitution of one or two amino acids at the N- and/or C-terminus of the single contiguous portion.

EPA is proposing to require that the virus used as the source of the coat protein sequence ''naturally infects plants that humans consume'' as an additional means of ensuring the proposed exemption is limited to PVCP-PIPs that fall within the base of experience discussed previously in this unit. This phrase is intended to limit the proposed exemption to residues of PVC-proteins that are already part of the normal human diet as naturally occurring plant virus coat proteins or are minimally modified from such proteins (see Unit IV.C.1.). The exemption would not extend to PVC-proteins encoded in part by sequences from animal or human viruses.

EPA proposes to define the term ''naturally infect'' to mean ''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 human dietary exposure. Viruses that may be able to infect plant species in a laboratory or greenhouse setting through manual infection may not ever infect such species in nature. EPA intends to include within this definition viruses that are likely to have been part of the human diet due to their ability to spread without intentional human intervention. 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 presence of natural virus coat proteins in food plants that humans consume. EPA therefore includes this mode of transmission in the definition of naturally infect to encompass those viruses that would be expected to be at

least occasionally found in the plant and therefore be a normal constituent of the human diet. To further clarify that the proposed exemption applies only to coat proteins from plant viruses, EPA is specifically including the word ''plant'' as an adjective in the name, i.e., ''PVC-proteins'' are ''plant virus coat proteins.''

EPA has considered whether to limit the proposed exemption to PVC-proteins from PVCP-PIPs based on viruses that naturally infect the *particular* food plant in which the PVC-protein is expressed. EPA must address whether there would be any safety issues raised from exposure to PVC-proteins if the virus used to create the PVCP-PIP does not naturally infect the particular plant species into which the PVCP-PIP is inserted. A PVC-protein may be expressed in a food plant that the virus does not naturally infect when heterologous resistance to a particular virus is conferred through a different virus' coat protein gene (e.g., Ref. 45). However, the Agency believes such PVC-proteins could be safely exempted from tolerance requirements because these proteins would still reasonably be expected to be part of the normal diet as long as they naturally infect plants used as food. Based on their broad host range, plant viruses are known generally to infect a wide variety of plants that humans consume. People generally eat a broad range of food plants through which they would reasonably be expected to be exposed to a wide variety of plant virus coat proteins (Ref. 12). In addition, EPA is not aware that any plant viral coat proteins have been identified as allergens, so it is unlikely that a person with food allergies avoids a particular food plant because of an allergic reaction to a viral coat protein. Based on this rationale and in the absence of contravening evidence, EPA concludes that a PVC-protein expressed in a plant that is not normally infected by the virus from which the PVC-protein was derived would raise no safety issues as long as the corresponding virus infects other plants that are consumed by humans.

When EPA asked the 2005 SAP to comment on this issue, the Panel ''expressed some disagreement as to whether the level of risk associated with human exposure to any protein is solely dependent on the protein itself. One Panel member concluded that the host producing the protein is of secondary importance. Others expressed concern related to expression of PVC-proteins in plants that are known to be highly allergenic such as peanut'' (Ref. 15). The Panel did not elaborate on the rationale for such concerns at this point in the SAP report. EPA's interpretation of this issue is that the concern is due to the possibility, articulated elsewhere in the Panel report, that ''the changed infectivity status of the plant may also induce changes in the overall protein expression pattern of the plant. Thus, in various tissues of the plant, natural plant proteins that have been identified as allergens may be expressed to a different, and in some cases, higher extent compared to a non-infected or a virus-infected plant without PVCP-PIP. In particular, pathogenesis-related (PR) proteins are known to be very inducible, and their expression levels may vary many-fold. Several pathogenesis-related proteins have been described as allergens (Breiteneder et al. 2000 and 2004), most notably the major birch pollen protein Bet v1 (Breiteneder et al. 1989). An increased expression of PR-proteins in pollen could increase both the risk of sensitization and the risk of elicitation of allergic reactions'' (Refs. 15, 46, 47, and 48). This concern is distinct from the concern that EPA addressed above, namely that the PVC-protein itself may introduce an allergen into a food source where it is not anticipated to be found. The issue the SAP raised would generally be addressed by the Food and Drug Administration (FDA) in evaluating food composition. However, EPA has not found evidence that introduction of a PVCP-PIP would affect induction of PR proteins *per se*. PR proteins are a normal constituent of plants because plants express such proteins in response to environmental stresses, including virus infection, exposure to certain chemicals, and wounding. Some plant tissues even constitutively express such proteins, e.g., those likely to be attacked by pests or exposed to environmental stresses such as ultra-violet (UV) irradiation (Ref. 49). Moreover, given the large number and variety of pathogens (including viruses) encountered by plants in the field, and given differences in the virus-infectivity status of plants that occur naturally, humans consume varying amounts of PR proteins as part of the normal diet. The level found in plants containing a PVCP-PIP is therefore expected to be within the range of natural variation.

EPA has also considered whether a geographic limitation on this proposed categorical exemption would be necessary to ensure that the exemption extends only to residues that are part of the U.S. diet; i.e., that the proposed exemption would only extend to PVC-proteins that are part of a PVCP-PIP constructed from a virus that occurs naturally in the United States. EPA believes that such a limitation is unnecessary to ensure that the PVC-proteins proposed for exemption fall within the base of experience supporting the proposal. Humans have long consumed viruses infecting food plants with no adverse effects. Given the extent of modern market practices in which food is shipped globally for human consumption, human dietary exposure to all viruses that infect food plants is likely to occur broadly. The lack of any known adverse effects attributable to plant viruses suggests that plant virus coat proteins in the diet are safe to humans.

EPA has also considered whether additional conditions are necessary to ensure that the expression level of virtually unmodified PVC-proteins found in plants is no greater than the level of plant virus coat protein generally found in a natural virus infection. The 2005 SAP suggested that ''for both modified and unmodified proteins, the Agency might wish to consider. . . expression levels'' when determining whether to exempt a PVC-protein from tolerance requirements (Ref. 15). The SAP apparently based this suggestion on the assumption that EPA considered exposure level to be an important component of a PVC-protein risk assessment given that the Agency's background material for the Panel indicated that the dietary exposure to PVC-proteins is anticipated to be similar to or less than the dietary exposure to plant virus coat proteins currently found in food plants naturally infected with viruses. However, even though EPA addresses exposure level in evaluating safety (e.g., see Unit IV.C.1.), the Agency also believes that the PVC-proteins that qualify for this proposed exemption are safe at any level that could be produced in a plant. Humans have been exposed to plant virus coat proteins over long periods of time at varying and sometimes high levels, and to date there is no indication that any plant virus coat protein is an allergen or a toxin. The Agency therefore believes that the hazard associated with PVC-proteins that are virtually unmodified from natural plant viral coat proteins is sufficiently low that it does not rise to the level warranting regulation, even if in some cases exposure to a PVC-protein might be greater than the exposure to the corresponding natural plant virus coat protein. Nevertheless, the Agency regards the anticipated low levels of exposure through food to the PVC-proteins covered by this proposal as additional support for this proposed categorical exemption. According to the 2005 SAP, ''On a per cell basis, it is

almost certain that all viral gene products are expressed at higher levels in virus-infected than transgenic plants'' (Ref. 15).

2. *Proposed exemption conditional on Agency determination.* The Agency recognizes that product developers frequently modify the genetic material of a PVCP-PIP, e.g., in order to achieve greater efficacy (Ref. 50) and that most of these changes would be unlikely to result in proteins affecting potential dietary risk. However, the Agency cannot at this time articulate a criterion that would ensure all PVC-proteins with such modifications fall within the base of experience supporting the proposed exemption.

The question of how to objectively define criteria on which the regulated community may rely to determine *a priori* how much a virus coat protein may be modified and still fall within the range of natural variation is a key challenge. EPA first considered the question of how to describe residues that fall within the base of experience supporting exemption when the Agency issued its proposal on November 23, 1994 (59 FR 60539). In the July 19, 2001 supplemental notice (66 FR 37865), EPA again addressed the question of how to describe PVCP-PIPs that fall within the recognized base of experience supporting the proposed categorical exemption.

In October 2004, the FIFRA SAP was asked to consider the degree and ways a plant virus coat protein gene might be modified while still retaining scientific support for the idea that humans have consumed the products of such genes for generations and that such products therefore present no new dietary exposures (Ref. 14). They responded, ''There was no clear consensus on how much change would be necessary to invalidate this assumption, although there was general agreement that the appropriate comparison is to the range of natural variation in the virus population.'' The 2005 SAP also addressed this question. They concurred that, ''it is extremely difficult to identify modifications that would be expected to be 'within the range of natural variation for all virus families'. . . . Given the possible range of natural variations for PVC proteins, it would be appropriate to assess whether specific modifications are within natural variation limits of the PVC protein on a case-by-case basis'' (Ref. 15).

EPA believes that developing objectively defined criteria on which the regulated community could rely to determine whether a modified PVC-protein falls within the natural range of variation for a particular virus is not currently feasible because the Agency knows of no generally applicable, established baseline for what constitutes the range of natural variation of a virus. EPA thus does not believe that proposing an exemption that would allow developers to self-determine eligibility of modified PVC-proteins would be supportable. Rather, EPA is proposing that under proposed § 174.477(b), the residues of such a PVC-protein would be exempt only if the Agency determines after review that the encoded PVC-protein is minimally modified when compared to an unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part.

In determining whether a PVC-protein is minimally modified from a natural viral coat protein, EPA will consider first how similar the PVC-protein is to a natural viral coat protein by evaluating information on the PVCP-PIP genetic construct, PVC-protein deduced amino acid sequence, and biochemical characterization of the PVC-protein as expressed in the plant (e.g., molecular weight to evaluate potential post-translational modifications). EPA might also evaluate developer-submitted analyses that characterize the PVC-protein sequence relative to the range of natural coat protein variation found in public sequence databases. Those PVC-proteins determined to be similar to a natural viral coat protein would be further evaluated to determine whether the modified PVC-protein is as safe as an unmodified protein by considering information from an amino acid sequence comparison with known protein toxins and allergens. The type and extent of information that would need to be provided in order for EPA to determine whether a PVC-protein is minimally modified and therefore qualifies for the exemption would be determined on a case-by-case basis.

The 2005 SAP identified certain modifications that might raise potential concerns when considering if a protein is minimally modified, including ''the addition or removal of protease recognition sites, the addition or removal of cysteine residues involved in internal cross-links, the addition or removal of proline residues that act as secondary structure 'break points,' and the addition or removal of asparagines and alanines involved in glycosylation'' (Ref. 37). By contrast, the report identified ''[m]odifications such as single amino acid substitutions with biochemically similar amino acids that do not affect secondary or tertiary structure'' as potentially being of relatively little concern (Ref. 37). EPA would consider this guidance as appropriate in evaluating individual exemption petitions to determine whether a protein is minimally modified.

Regarding the 2005 SAP suggestion that EPA might wish to consider expression levels in determining whether to exempt a PVC-protein from tolerance requirements, the Agency believes that such an evaluation is not necessary to determine whether a PVC-protein is minimally modified. EPA would necessarily have to find such proteins to be similar to a natural viral coat protein in order for them to qualify for this proposed exemption. EPA believes that minimally modified PVC-proteins are safe at any level for the same reasons discussed above for virtually unmodified proteins (Unit IV.E.1.). In both cases, the hazard associated with PVC-proteins qualifying for this proposed tolerance exemption is sufficiently low that it does not rise to the level warranting regulation, even if in some cases exposure to a PVC-protein might be greater than the exposure to the corresponding natural plant virus coat protein. (However, see Unit XI. for a discussion of how exposure level could possibly be considered under the proposed exemption structure when reviewing minimally modified proteins.)

Under proposed § 174.477(b), the procedures for obtaining a determination that a PVC-protein fits under the tolerance exemption would be no different than those currently provided under the statute for obtaining a tolerance exemption. A person can file a submission requesting a determination (21 U.S.C. 346a(d)) of whether a particular PVC-protein fits under the tolerance exemption, or the Agency can initiate an action to issue a determination (21 U.S.C. 346a(e)). After a person files a submission under FFDCA section 408(d)(1) proposing that a particular PVC-protein falls under this exemption because it is minimally modified from a natural plant virus coat protein, FFDCA section 408(d)(3) requires that the Administrator determine whether a petition meets the requirements of the statute and publish a summary of the petition and other required information in the **Federal Register** within 30 days of making that determination. Alternatively, the Administrator may publish a notice of proposed rulemaking and provide a period of generally not less than 60 days for public comment. In either case, EPA will publish any final rule exempting a PVC-protein from the requirement of a tolerance in the **Federal Register** and allow 60 days for any person to file objections thereto (21 U.S.C. 346a(g)(2)).

Currently no fees would be associated with either the proposed categorical exemption under § 174.477(a) or the Agency's determination under proposed § 174.477(b) that a particular PVC-protein fits under the tolerance exemption.

For residues of a PVC-protein that would not qualify for this proposed exemption under either § 174.477(a) or (b) because the Agency cannot determine that the encoded PVC-protein is minimally modified from an unmodified coat protein from a virus that naturally infects food plants, an applicant may petition the Agency for an individual tolerance exemption under FFDCA section 408 (see also 40 CFR 180.7).

F. Tolerance Issues Associated with Unintended Protein Production when Virus Resistance is Mediated through Post-Transcriptional Gene Silencing

Section 408 of the FFDCA does not require a tolerance or tolerance exemption if residues will not be present in food moving in interstate commerce. However, with the exception of residues that meet the requirements proposed at § 174.477(a), the mere fact that a developer may not detect residues during product development will not protect the food from seizure if residues are subsequently found following commercialization, either because detection techniques improve or because the protein is unexpectedly produced. If such an event occurs and no tolerance exemption exists for residues of that PVC-protein (regardless of its safety), any food containing the PVC-protein residues would be adulterated and subject to seizure. In addition, any FIFRA exemption that may have been applicable for the PVCP-PIP would no longer be valid because 40 CFR 174.21(b) would no longer be satisfied. Any sale or distribution of such a PVCP-PIP would constitute sale and distribution of an unregistered pesticide, in violation of FIFRA section 12(a)(1).

The 2005 SAP suggested that the construction of certain PVCP-PIPs may offer a reasonable level of assurance that PVC-protein production would not occur, i.e., transgene insertions where the transcribed segment lacks an initiator codon or insertions of transcribed inverted repeat constructs that constitutively produce transcripts that are folded into double-stranded RNA as the immediate product of transgene transcription (Ref. 15). However, for other types of constructs, questions remain about circumstances under which PVC-protein might be detected and/or produced in food at some point after commercialization even though PVC-protein may not have been detected and/or produced during product development. For example, it is known that in some cases PTGS must be triggered before transgene RNA production can be effectively suppressed. Lindbo *et al.* (Ref. 51) used tobacco etch virus (TEV) to infect transgenic tobacco plants containing a TEV coat protein gene. Plants temporarily developed symptoms but were able to recover from infection. Recovered transgenic plant tissue showed significantly reduced levels of transgene mRNA, and PVC-protein was undetectable. However, plant tissues unchallenged with virus did express PVC-protein, suggesting that in at least some cases of PTGS-induced virus resistance, PVC-protein may be produced until virus infection occurs. Béclin et al. (Ref. 52) showed that in transgenic tobacco lines expressing a β-glucuronidase (uidA) transgene, suppression of transgene expression always occurs but is initiated at different plant developmental stages: Either 15 days after germination or 2 months post-germination. Prior to PTGS initiation, transgenic protein is expressed, suggesting that in at least some cases lack of protein production may only occur after a certain developmental stage is reached. Likewise, Pang *et al.* (Ref. 53) found that plant developmental stage plays an important role in the timing of PTGS initiation.

Experiments demonstrating that plant developmental stage determines PTGS initiation suggest that any environmental factors influencing plant growth would also affect the amount of time before RNA and protein production is effectively suppressed. At least one experiment has looked more directly at the influence of environmental factors on PTGS. Szittya *et al.* (Ref. 54) demonstrated that cold temperatures inhibited transgene-induced RNA silencing leading to increased levels of transgene mRNA, although they did not report on the level of transgenic protein.

In addition to temporal changes in protein production that may be influenced by varying environmental conditions, PTGS may also be associated with variation in protein expression across different plant tissues. Plant lines expressing a nitrate reductase transgene were found to display PTGS in leaves and stem tissue but not in shoot apical or axillary meristems (Ref. 52). As in other experiments (Ref. 51), transgene protein was not detectable and transgene mRNA levels were significantly reduced in plant tissue displaying PTGS. However, plant tissue in which gene silencing does not occur showed normal levels of transgene mRNA, and transgenic protein was produced.

It has been shown that PTGS can be suppressed by viruses that encode certain suppressor proteins leading to loss of the virus-resistant phenotype conferred by a PVCP-PIP. For example, Savenkov and Valkonen (Ref. 55) showed that resistance to Potato virus A (PVA) in *Nicotiana benthiana* could be overcome when plants were challenged with Potato virus Y (PVY). Although levels of transgene mRNA in healthy transgenic plants were extremely low or below the detection limit, transgene mRNA was readily detectable in PVY-infected plants where suppression of gene silencing had apparently occurred. The study did not report whether PVC-protein was produced from the transgene mRNA.

The 2005 SAP was asked to comment on issues associated with protein production in the case of plants containing a PVCP-PIP that confers resistance through an RNA-mediated mechanism. The Panel responded that ''[g]iven the wide variety of conditions that can modulate the transition from PTGS to no PTGS for non-[inverted repeat (IR)] transgenes. . .it is likely that a non-IR transgene insertion that retains an initiation codon for protein synthesis will make at least a low level of protein in at least some plant tissues over the course of its development, especially in the field where there is exposure to environmental extremes and virus infections. Thus, these PVCP-PIP plants may accumulate virus-derived mRNA and proteins in these situations'' (Ref. 15). EPA notes that the Panel further concluded that ''[b]ecause of low levels of accumulation and sequence identity to the natural viral pathotypes. . .these PVCP-PIPs pose similarly low risks'' as PVCP-PIPs that produce no protein (Ref. 15). However, any PVC-protein residue in food that is not covered by a tolerance or tolerance exemption would constitute an adulterant of the food supply irrespective of the protein's safety or the level at which it is detected.

The above considerations suggest that many factors should be considered in making a determination of whether residues of a PVC-protein will be present in food derived from a crop containing a PVCP-PIP. Due to the serious consequences of having an unapproved residue in the food supply (as discussed earlier in this unit), EPA strongly recommends that developers consult with the Agency before determining that no tolerance or tolerance exemption for the PVC-protein

would be necessary based solely on the premise that no residues of the protein are anticipated to be present. EPA expects that the Agency would conclude no PVC-protein tolerance exemption would be necessary for insertion events where the transgene either lacks an initiation codon for protein synthesis or is inserted in an inverted-repeat orientation, provided that evidence is given to the Agency to verify the characteristics of the insertion event. For such constructs, the 2005 SAP indicated the PVCP-PIP ''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. 15).

For all other types of PVCP-PIP insertion events, EPA is considering several approaches under FFDCA for PVC-proteins that are not readily detectable, but which the SAP indicated would likely be produced under some circumstances (Ref. 15), some of which might result in the PVC-protein being in food. EPA does not currently have a preferred approach and presents several options to promote full consideration of the issues. These options are not necessarily mutually exclusive, and the approach pursued may vary depending on the characteristics of the PVCP-PIP under consideration. The discussion below relates only to proteins that EPA review would determine to be minimally modified, i.e., proteins that are similar, but not identical to natural plant virus coat proteins. Virtually unmodified PVC-proteins would be covered under the proposed tolerance exemption without any Agency action. The discussion is not relevant to proteins that would not be able to qualify under this proposal as either virtually unmodified or minimally modified because the proposed tolerance exemption would not cover such proteins regardless of how EPA implements the exemption.

Under one approach, when no PVC-protein is detected during product development, EPA would *not* issue a determination of whether the PVC-protein is minimally modified (and therefore falls under this proposed tolerance exemption). Section 408 of FFDCA does not require a tolerance or tolerance exemption for foods that do not bear any residues, and such an approach would be consistent with current EPA practice regarding chemical pesticide residues in that tolerance determinations are not generally issued for substances when residue studies demonstrate that detectable residues will not be present in food. However, if food is subsequently found bearing residues of the PVC-protein, that food would be adulterated and subject to seizure unless and until EPA could make a determination that the PVC-protein is minimally modified and is therefore covered by this proposed tolerance exemption.

Any adulterant in the food supply would likely cause public concern and great expense—whether or not the PVC-protein were subsequently determined to be safe. The Agency also notes that these costs are not necessarily borne by the product developer, but rather may disproportionately affect farmers and/or food producers because any adulterated food would be subject to seizure or recall. The Agency is considering this approach under the assumption that the absence of detectable protein using rigorous testing could give reasonable assurance that PVC-protein residues would not be found in food and therefore a tolerance determination would be unnecessary to prevent adulteration of the food supply. EPA would expect developers to provide the Agency with data acquired during product development that demonstrates no PVC-protein residues in food would be reasonably anticipated during the commercial life of the PVCP-PIP. For example, such data could be obtained by testing for protein and/or mRNA production in all plant tissues and all developmental stages that are harvested for food production under a variety of circumstances and environmental conditions representative of those that the plant may experience during its commercial cultivation. Challenge with a known PTGS suppressor protein introduced by a replicating virus vector, genetic crosses, or agro-infiltration (Ref. 56) may also in some cases be a sufficient and less burdensome technique to show that no PVC-protein is able to be translated from the PVCP-PIP. The potential to elicit protein production from silenced transgenes has been shown by studies investigating whether particular proteins are able to suppress such silencing (Ref. 56). The 2005 SAP discussed such a technique, indicating that ''[t]o determine if PTGS-based PVCP-PIP plants have the potential to produce proteins, the most effective test is to use viral suppression of PTGS. In this type of assay, the PVCP-PIP plants are infected with viruses from the potyvirus, cucumovirus, and tombusvirus genera. These viruses encode different classes of PTGS suppressor proteins. . . Protein and RNA are then extracted from the infected plant tissue and assayed for the presence of the PVCP-PIP accumulated full-length RNA and protein. Standard tests for protein detection are ELISA and immunoblot ('Western' blot) analyses with specific antibodies. Triplicate experiments should be sufficient to determine that the results of these tests are reproducible'' (Ref. 15). Given that FFDCA does not require a developer to demonstrate that no tolerance exemption is necessary, EPA would require such testing as a condition of either registering or exempting the PVCP-PIP under FIFRA.

If the developer detects a PVC-protein during the course of investigating potential PVC-protein production, e.g., through challenge with a suppressor protein, this protein would only be covered under the proposed categorical tolerance exemption, i.e., without any Agency action, if the protein falls within the definition of a virtually unmodified PVC-protein. Therefore, unless the protein is virtually unmodified from a natural plant virus coat protein, EPA would expect a developer to provide the Agency with information for a determination of whether the PVC-protein qualifies as minimally modified and meets the proposed conditional tolerance exemption. (See Unit IV.E.2. for a discussion of the factors EPA intends to consider in making this determination.)

When possible, EPA would expect to see biochemical characterization of the PVC-protein. However, EPA recognizes that such characterization may be difficult or even impossible in some cases. For example, when only very low levels of protein are produced, it may be difficult to obtain sufficient amounts of protein for biochemical characterization. In addition, EPA recognizes the cost and burden of producing sufficient protein for such characterization may not be warranted for PVC-proteins given that an evaluation based on the construct sequence alone could consider most of the issues EPA intends to evaluate when determining whether a PVC-protein is minimally modified (see Unit IV.E.2.).

EPA is therefore also considering a second approach to addressing PVC-proteins that are not detected during product development but whose presence as residues in food cannot be ruled out for the commercial life of the PVCP-PIP. Under this approach, EPA would evaluate the PVC-protein to determine whether it qualifies as minimally modified from a natural plant virus coat protein and is thus eligible for this proposed tolerance exemption based only on its amino acid sequence as deduced from the sequence of the inserted gene. EPA notes the advice of the 2005 SAP that ''[i]t is critical to evaluate the protein as expressed in the

host, including factors such as post-translational modifications'' (Ref. 15). Nevertheless, EPA considers evaluating the protein as expressed in the host to be less important for minimally modified PVC-proteins than for many other types of proteins. A PVC-protein would not be expected to have significantly different post-translational modifications than a plant virus coat protein produced in a virus-infected plant. Because plant viruses replicate in plant cells as part of their normal life cycle, any post-translational modifications are expected to be the same for a PVC-protein expressed from a plant transgene as for a plant virus coat protein expressed from a viral genome in a virus-infected plant.

As a third alternative, EPA is considering whether the Agency could expand this proposed tolerance exemption to cover all PVC-proteins that would be produced from constructs where resistance is demonstrated to EPA to be mediated through PTGS, e.g., those that confer virus resistance in the absence of detectable protein production for at least some period of time. The rationale for this alternative would be, as indicated by the 2005 SAP, that ''PTGS-based virus resistance requires greater than 90% RNA sequence homology between the PVCP-PIP transgene and the target virus, indicating that the viral mRNA and protein produced in PVCP-PIP plants will be nearly identical to the viral pathotype that occurs in the United States'' (Ref. 15). To implement this alternative, the Agency would have to be able to conclude, without any case-by-case examination, that any PVC-protein produced from a PVCP-PIP that mediates resistance through PTGS would be safe. Even if a PVC-protein were detected before product deployment, such a protein would not need any evaluation by the Agency in order to be covered by this tolerance exemption. The rationale for this approach would be that any such PVC-protein would meet the conditions of a minimally modified protein (as discussed in Unit IV.E.2.) given the necessity for transgene transcript sequence similarity to natural plant virus coat protein sequences in order for PTGS to effectively function. Although EPA does not believe it could identify *a priori* which modifications would be within the range of natural variation for the protein, under this rationale the induction of PTGS would be an *a priori* indicator that such a PVC-protein is within the range of natural variation of the protein. The 2005 SAP suggested that all PTGS-based PVCP-PIPs would ''pose similarly low risks'' as those that would have no protein expression under any circumstances (Ref. 15), giving scientific support for this option. However, the Agency notes that this advice is not entirely consistent with advice regarding PVC-protein safety received by the Panel. For one, both the 2004 and 2005 SAPs were unable to endorse a tolerance exemption for PVC-proteins other than those that are virtually unmodified from a natural plant virus coat protein unless the Agency performed a case-by-case review of some nature. PVC-proteins could be encoded for by a nucleic acid sequence that meets the 90% similarity required for PTGS to function but fail to be virtually unmodified from a natural virus coat protein (see Unit IV.E.1.). Moreover, the 2005 SAP recommended 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'' (Ref. 15). While PTGS requires a relatively high sequence similarity with natural virus coat proteins to function, only a portion of the coat protein gene is necessary, suggesting that many truncated proteins would be encompassed in this exemption without any review of whether they occur naturally. (See, however, EPA's discussion of whether truncated proteins could be determined to be exempt without Agency review in Unit IV.E.2.) The 2005 SAP also suggested that a low level of protein expression would indicate low risk, but prior SAPs and other scientific experts have been unable to establish a threshold below which the level of protein would not present concerns with respect to food allergenicity (Refs. 57 and 58).

V. Toxicological Profile

Consistent with section 408(b)(2)(D) of FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this proposed action and considered its validity, completeness, and reliability and the relationship of this information to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children.

EPA's risk assessment was based primarily on an analysis of human experiences with the breeding and cultivation of agricultural plants as well as food preparation and consumption. EPA combined human experience in consuming food containing coat proteins from viruses that naturally infect plants with knowledge of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry, and plant breeding to evaluate the potential risks of the residues of PVC-proteins qualifying for this proposed exemption.

EPA considered the nature of any toxic effects that might be caused by residues of PVC-proteins proposed for exemption. As mentioned above, coat proteins from plant viruses that naturally infect plants are widespread in foods (Refs. 6, 7, and 10) and are not associated with toxic or pathogenic effects in humans or vertebrates (Refs. 18 and 19). Residues of PVC-proteins qualifying for this proposed exemption are virtually unmodified or minimally modified from other coat proteins from viruses that naturally infect food plants and that have been safely consumed for hundreds if not thousands of years. Given this long history of safe use and the fact that toxicity is an unusual property among proteins in general (Ref. 59), consumption of food containing residues of PVC-proteins qualifying for this proposed exemption is not expected to present a toxic effect on humans or animals.

EPA considered the available information on the various dietary consumption patterns of consumers and major identifiable consumer subgroups as it pertains to residues of PVC-proteins in food. Plant virus coat proteins are, and always have been, widespread in all food from crop plants since most plants are susceptible to infection by one or more viruses. Thus, all consumers and all major identifiable consumer subgroups are, and have been, exposed to plant virus coat proteins. Implementation of this proposed exemption is not expected to alter the current consumption patterns of plant virus coat proteins except perhaps to reduce exposure through a decrease in virus-infected plants. Therefore, EPA does not expect any special sensitivities to arise due to the consumption of residues of PVC-proteins that are proposed to be exempted.

VI. Aggregate Exposures

In examining aggregate exposure, section 408 of FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

EPA considered the available information on the likely aggregate exposure level of consumers to PVC-proteins qualifying for this proposed exemption and to other related substances, including exposures to plant virus coat proteins occurring through natural processes such as viral infection of a food plant. This analysis included a consideration of exposures from dietary sources as well as from other non-occupational sources.

The PVC-proteins qualifying for this proposed exemption and plant virus coat proteins that occur naturally are both produced in living plants and are subject to the natural processes of degradation and decay that all biological materials undergo. They are broken down by enzymatic processes of living organisms into constituent parts that are used as building blocks for other biological substances (Ref. 60). Because of their biodegradable nature, neither PVC-proteins nor naturally occurring plant virus coat proteins 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). Humans ingesting naturally occurring plant virus coat proteins and residues of PVC-proteins qualifying for this proposed exemption in food are likely to quickly degrade them and use their constituent elements as nutrients.

Because of these characteristics, there is limited potential for exposures to PVC-proteins qualifying for this proposed exemption beyond direct physical exposure to a plant. In most cases, the predominant exposure route will be dietary. In general, EPA anticipates that dietary exposure to PVC-proteins qualifying for this proposed exemption through human and animal consumption of plants expressing PVC-proteins will be similar to, or less than the amounts of plant virus coat proteins currently consumed through food plants that are infected naturally with viruses (see Unit IV.C.1.). Exposure through other routes is unlikely because the substances are in the plant tissue and thus are found either within the plant or in close proximity to the plant. EPA expects non-dietary exposure (i.e., non-food oral, dermal, and inhalation) in non–occupational settings to be negligible.

A. Dietary Exposure

EPA considered the consequences of dietary exposure to PVC-proteins that are the subject of this proposed exemption. A large base of experience exists, including information on human dietary exposure, for foods that contain coat proteins from viruses that naturally infect plants. As plant virus coat proteins are ubiquitous in food, EPA concluded that all humans are exposed to plant virus coat proteins throughout their lives as part of their diet. Neither naturally occurring plant virus coat proteins nor the PVC-proteins qualifying for this exemption are toxic, and there is no evidence that consumption in food of residues of PVC-proteins qualifying for this proposed exemption would lead to any harm.

1. *Food*. As mentioned in Unit IV.C.1., the Agency has concluded that dietary exposures to PVC-proteins qualifying for this proposed exemption will be similar to or less than the amounts of plant virus coat proteins currently found and consumed in food plants that have been naturally infected by viruses. Even if there were notable exposure to PVC-proteins, there is no evidence that PVC-proteins are toxic to humans. Moreover, the Agency is not aware of any coat protein from a virus that naturally infects plants that has been identified as a food allergen for humans. The residues that are proposed to be exempted by this **Federal Register** document would not differ substantially from residues of naturally occurring plant virus coat proteins.

2. *Drinking water exposure*. EPA also evaluated potential non–occupational exposures in drinking water. Residues of PVC-proteins that qualify for this proposed exemption are produced inside the plant itself. When the plant dies or a part is removed from the plant, microorganisms colonizing the tissue immediately begin to degrade it using the components of the plant tissue (including residues of PVC-proteins) as building blocks for making their own cellular components or for fueling their own metabolisms. PVC-proteins and naturally occurring plant virus coat proteins are subject to the same processes of biodegradation and decay that all biological materials undergo and are not known to either bioaccumulate or biomagnify (Ref. 60). Even if they were to reach surface waters (e.g., through plant parts or pollen falling into bodies of water), they are unlikely to present anything other than a very negligible exposure in drinking water drawn either from surface water or ground water sources due to biodegradation of these residues.

B. Other Non-Occupational Exposure

Residential exposure to PVC-proteins qualifying for this proposed exemption would be limited. Residential exposure could occur through use of PVCP-PIPs in ornamental plants or in plants grown in home gardens. Such exposure to PVC-proteins is expected to be negligible on a per-person basis compared to exposure to PVC-proteins and natural plant virus coat proteins in the diet. Furthermore, PVC-proteins qualifying for this exemption would not be toxic, and there is no evidence that exposure to such PVC-proteins would lead to any harm.

1. *Dermal exposure*. Residues of PVC-proteins qualifying for this proposed exemption may be present in sap or other plant exudates and thus may present some limited opportunity for dermal exposure to persons coming physically into contact with the plant or raw agricultural food from the plant. Individuals preparing meals are those most likely to experience dermal contact with the residues on a non-occupational basis. As noted by the 2005 SAP, PVC-proteins' ''natural exposure route may be via oral ingestion. However, genetically modified expression of PVCP-PIPs would lead to the presence of [PVC-proteins] in other plant compartments such as pollen grains which lead to other sites of exposure including respiratory and cutaneous surfaces'' (Ref. 15). However, the potential amount involved in such exposure on a per person basis is likely to be negligible in comparison to potential exposure through the dietary route to PVC-proteins and natural plant virus coat proteins (Ref. 61). Moreover, PVC-proteins qualifying for this proposed exemption or naturally occurring plant virus coat proteins that occur in food are unlikely to cross the barrier provided by the skin (Ref. 62).

2. *Inhalation exposure*. Pollen could potentially contain residues of PVC-proteins qualifying for this proposed exemption. Individuals (e.g., those visiting, living, or working near enough to farms, nurseries, or other plant-growing areas to be exposed to wind-blown pollen) may be exposed to the pollen through inhalation. On a per person basis, the potential amount of pollen involved in these exposures is likely to be negligible in comparison to potential exposure through the dietary route (Ref. 61). Some members of the 2005 SAP indicated that ''[i]ntroduction of new proteins to pollens and other plant materials may have the potential to cause problems, and consideration by the Agency is warranted'' (Ref. 15). As the Panel explained, ''While plant viruses systemically infect plant tissues, there is tissue specific regionalization of viruses. Therefore [plant virus coat proteins] would be restricted within certain compartments. Transgenic expression of some PVC-PIPs would

promote [PVC-protein] expression in different plant tissues relative to what would naturally occur (i.e., all cells). This could lead to heightened levels of [PVC-proteins] in certain tissues (i.e., pollen grains) and the effects (specifically to allergenicity) are not yet known. This has implications for non-dietary exposure of plant proteins. In some instances, [plant virus coat protein's] natural exposure route may be via oral ingestion. However, genetically modified expression of PVCP-PIPs would lead to the presence of [PVC-proteins] in other plant compartments such as pollen grains which lead to other sites of exposure including respiratory and cutaneous surfaces'' (Ref. 15). However, other Panel members felt that ''unless there is evidence that PCVP-PIPs are expressed on the surface of pollen grains in a manner different from expression in wild-type plants, the risk of increased allergy from exposure to pollen is non-existent'' (Ref. 15). The Agency also notes that in order for expression of a PVC-protein to be a concern, the protein would have to be expressed on the surface of the pollen grain, it would have to actually be an antigenic protein, and it would have to elicit an allergic response through secondary exposure. The Agency considers that this sequence of events is very unlikely to occur, in part because no plant virus coat proteins have been identified as being allergenic, and PVC-proteins qualifying for this exemption are virtually unmodified or minimally modified from natural plant virus coat proteins. Therefore, it is unlikely that inhalation exposure to PVC-proteins in pollen would result in adverse effects.

VII. Cumulative Effects

EPA examined the available information on residues of PVC-proteins qualifying for this proposed exemption for cumulative effects with other substances, including natural plant virus coat proteins. Plant virus coat proteins are nontoxic proteins that are widespread in food from plants. They have not been associated with toxic effects to animals or humans (see Unit IV.C.3.). EPA is therefore not aware of any other substances that could have a common mechanism of human toxicity with residues of PVC-proteins qualifying for this exemption and cannot identify any cumulative effects of such residues with any other substances.

VIII. Safety Factor for Infants and Children

A. In General

Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the information base on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

B. Prenatal and Postnatal Sensitivity

EPA considered available information on the dietary consumption patterns of infants and children as it pertains to residues in food of PVC-proteins qualifying for this proposed exemption. The range of foods consumed by infants and children is in general more limited than the range of foods consumed by adults. Most newborns rely on breast milk or formula-based products for nutrition, although some infants are fed soy-based products. Infants may begin as early as 4 months of age to consume solid foods that are based on foods consumed by the general adult population albeit in different proportions and with processing to facilitate swallowing. As infants and children mature, more and more of the foods normally consumed by adults become part of their diets, and the relative proportions of the different types of food consumed change to more closely resemble an adult diet. Because plant viruses are ubiquitous in plant foods, EPA concluded that infants and children are exposed to plant virus coat proteins from the time they begin to eat food of plant origin. As the diets of humans change from infancy through childhood and into adulthood, there is some possibility that the amount of plant virus coat proteins being consumed may change, with those consuming the greatest amounts of food of plant origin most likely exposed to the most plant virus coat protein. However, there is no evidence that such changes are likely to result in disproportionately high consumption of foods containing plant virus coat proteins among infants and children in comparison to the general population. Furthermore, PVC-proteins qualifying for this proposed exemption are not toxic, and there is no evidence that any amount of exposure to such PVC-proteins in food would lead to any harm.

EPA considered available information on the potential for special susceptibility of infants and children, including prenatal and postnatal toxicity, to residues of PVC-proteins qualifying for this proposed exemption. PVC-proteins in food are not toxic. There is no scientific evidence that residues of such PVC-proteins in food would have a different effect on infants and children than adults due to neurological differences between infants, children, and adults.

The Agency's consideration of cumulative effects of the residues of PVC-proteins qualifying for this proposed exemption on the general population also included consideration of effects for infants and children. Neither naturally occurring plant virus coat proteins nor PVC-proteins qualifying for this proposed exemption are toxic when consumed as part of the diet, and EPA is not aware of any substances that might have a common mechanism of toxicity with these PVC-proteins. There is no scientific evidence indicating any potential for adverse effects on infants and children due to cumulative exposure to residues of such PVC-proteins. EPA concludes that there is no evidence of a common mechanism of toxicity between PVC-proteins qualifying for this proposed exemption and any other substances, and therefore, no cumulative effects of these PVC-proteins would reasonably be anticipated.

C. Conclusion

There is a complete toxicity base of information for PVC-proteins that are the subject of this proposed exemption, and exposure data are estimated based on data that reasonably account for potential exposures. For residues of PVC-proteins qualifying for this proposed exemption, EPA has determined that a tenfold margin of safety is not necessary to protect infants and children. As noted in Unit IV.C., EPA based its assessment of exposure and toxicity on the long history of safe human and animal consumption of food containing plant virus coat proteins. EPA also relied upon information from the disciplines of plant genetics, plant physiology, plant virology, microbial ecology, ecology, biochemistry, molecular biology, and plant breeding. Based on all of this information, EPA concludes that PVC-proteins qualifying for this proposed exemption in food are not toxic and may be safely consumed, including by infants and children. There is no evidence that exposure to such

PVC-proteins in food, including changes in exposure because of changes in the relative proportions of the different types of food consumed from infancy through childhood and into adulthood, leads to any harm. Thus, on the basis of valid, complete, and reliable information, EPA has concluded that residues in food of PVC-proteins qualifying for this proposed exemption are safe for infants and children and that an additional margin of safety need not be applied.

IX. Other Considerations

A. Endocrine Disruptors

Based on available information that plant virus coat proteins are ubiquitous in foods and have no known adverse effects when consumed as part of the diet (see Unit IV.C.), EPA does not expect residues of PVC-proteins qualifying for this proposed exemption to cause estrogenic or other endocrine effects. In the May 16, 1997 supplemental document, EPA specifically requested comment on PVC-proteins causing estrogenic effects. No information was received indicating that either naturally occurring plant virus coat proteins or PVC-proteins that qualify for this proposed exemption might cause estrogenic or other endocrine effects. If EPA becomes aware of a potential for estrogenic or endocrine effects from exposure to residues of such PVC-proteins, the Agency will reexamine this proposed tolerance exemption in light of that information.

B. Analytical Method(s)

EPA has concluded that even though methodology exists to detect residues of PVC-proteins (Refs. 63, 64, and 65), there is no need to employ a practical method for detecting and measuring the level of residues of PVC-proteins qualifying for this exemption. There is no reason to believe that the residues of PVC-proteins proposed to be exempted in this **Federal Register** document would behave any differently than naturally occurring plant virus coat proteins in food. There is a reasonable certainty that no harm will result from exposure to any amount of residues in food of such PVC-proteins. Because these residues may be present in food at any level without causing harm, EPA has concluded that an analytical method is not required for detecting and measuring the level of residues of these PVC-proteins in food. EPA consulted with the Department of Health and Human Services (HHS) in making this determination.

C. Codex Maximum Residue Level

There are no Codex maximum residue levels established for PVC-proteins.

X. Preliminary Determination of Safety for U.S. Population, Infants, and Children

Based on the information discussed in this document and that discussed in the 1994 **Federal Register** documents, the supplemental documents, and the associated record as described in Unit XII.B., EPA preliminarily concludes that there is a reasonable certainty that no harm will result to the U.S. population, infants, and children from aggregate exposures to residues of PVC-proteins that qualify for this proposed exemption. Many years of experience with growing, preparing, and consuming food from plants containing plant virus coat proteins and information generated through years of study of the food supply (Refs. 6, 7, 8, 9, 10, and 66) indicate that adverse effects due to aggregate exposure to PVC-proteins qualifying for this proposed exemption through dietary, non-food oral, dermal, and inhalation routes are highly unlikely.

XI. Request for Comment

EPA requests comment on whether this proposed tolerance exemption identifies those PVC-proteins that are unlikely to result in new dietary exposures. When commenting, please use the terminology conventions adopted in this document, i.e., use ''plant virus coat protein'' when referring to the protein produced naturally from a plant virus, and use ''PVC-protein'' when referring to the protein component of a PVCP-PIP. The Agency requests comment on the following specific issues:

1. EPA requests comment on the options discussed in Unit IV.E.1. for defining virtually unmodified. Under the Agency's proposed rule, virtually unmodified proteins would be exempt from the requirement of a tolerance without Agency review. Under one option, virtually unmodified would be defined as 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. However, the Agency is considering removing the limitations on which amino acids may be added and on the number of amino acids that may be truncated from either end of a PVC-protein.

2. In addition to the types of changes discussed in the paragraph above, EPA requests comment on whether any other class of potential PVC-protein modifications (e.g., a particular number of amino acid substitutions) would always be expected to produce a PVC-protein as safe as an unmodified plant virus coat protein such that the protein would not warrant a case-by-case Agency review for a tolerance exemption. The Agency also requests that commenters indicate whether the number and combination of such modifications has any relevance to the product's safety. In October 2004, the FIFRA SAP was asked to consider the degree and ways a plant virus coat protein gene might be modified while still retaining scientific support for the idea that humans have consumed the products of such genes for generations and that such products therefore present no new dietary exposures (Ref. 14). They responded that ''[t]here was no clear consensus on how much change would be necessary to invalidate this assumption, although there was general agreement that the appropriate comparison is to the range of natural variation in the virus population.'' This question was also addressed by the 2005 SAP which concurred that ''it is extremely difficult to identify modifications that would be expected to be 'within the range of natural variation for all virus families'. . . Given the possible range of natural variations for PVC proteins, it would be appropriate to assess whether specific modifications are within natural variation limits of the PVC protein on a case-by-case basis'' (Ref. 15). Commenters should specifically address this advice when formulating comments.

3. EPA requests comment on whether there would be any safety issues associated with exposure to PVC-proteins if the virus used to create the PVCP-PIP does not naturally infect the particular plant species into which the PVCP-PIP is inserted. A PVC-protein may be expressed in a food plant that the virus does not naturally infect when heterologous resistance to a particular virus is conferred through a different virus' coat protein gene (e.g., Ref. 45). Such PVC-proteins could be safely exempted from tolerance requirements if these proteins are reasonably expected to be part of the current diet, as discussed in Unit IV.E.1. In light of the uncertainty surrounding the SAP's remarks concerning this issue (see Unit IV.E.1.), EPA requests comment on whether there would be any safety issues associated with exposure to*the*

PVC-proteins themselves if the virus used to create a PVCP-PIP does not naturally infect the particular plant species into which the PVCP-PIP is inserted.

4. EPA requests comment on whether the Agency should consider the level of PVC-protein expression in determining whether a PVC-protein is virtually unmodified or minimally modified and thus exempt from tolerance requirements. EPA concurs with the 2005 SAP that ''exposure level is an important component of an allergenicity risk assessment'' (Ref. 15). However, it can be argued that PVC-proteins that are virtually unmodified or minimally modified when compared to natural plant viral coat proteins are of sufficiently low hazard that the potential risk does not rise to the level warranting regulation, even in the rare case that exposure to a PVC-protein might be greater than the exposure to the corresponding natural plant virus coat protein. Although EPA's review of PVC-proteins to determine if they are minimally modified could allow the Agency to consider PVC-protein expression level relative to natural levels of plant virus coat proteins, the Agency is unsure how this factor could be readily incorporated into the criteria for a developer-determined tolerance exemption; EPA anticipates needing to consider the appropriateness of data designed to address these questions on a case-by-case basis. Therefore, if protein expression level is considered a necessary factor in evaluating whether to exempt a virtually unmodified PVC-protein from tolerance requirements, EPA seeks comment on how such considerations could be articulated in a clear, unambiguous criterion.

5. EPA requests comment on the Agency's options for how to view a PVC-protein that would not meet the definition of virtually unmodified and is not detected during product development if the construct suggests that its production is likely to occur in at least some plant tissue at some point in time (see Unit IV.F.). Specifically, EPA requests comment on the relative costs and benefits of allowing a PVCP-PIP that does not produce detectable PVC-protein residues in food during product development to be sold or distributed without a PVC-protein tolerance exemption in place. EPA is particularly interested in information about the likelihood that protein would fail to be detected during product development but subsequently be detected in food. The Agency is also interested in comments on conditions under which protein detection protocols could be conducted to provide adequate assurance that such events would not occur, e.g., any key environmental parameters that should be varied during testing.

EPA also requests comment on whether obtaining characterization data of a plant-produced PVC-protein for a tolerance review is scientifically feasible in all cases where the PVCP-PIP insertion event contains a translation initiation codon and is not present in an inverted repeat orientation. The Agency would like to know for any given crop how technically difficult it would be to attempt to induce protein production through challenge with a known PTGS suppressor protein, e.g., through introduction by a replicating virus vector, genetic crosses, or agro-infiltration (Ref. 56). In addition, EPA would like to know how likely it is that such techniques could yield sufficient quantities of PVC-protein for analysis (e.g., mass spectrometry or glycosylation analysis). The Agency would also be interested in hearing of additional techniques that could be employed to obtain plant-produced PVC-protein in cases where PTGS normally prevents accumulation of protein but is not expected to be consistently activated, thereby leading to PVC-protein production.

Regarding the second alternative presented for PVC-proteins associated with PTGS, EPA requests comment on the value of the additional information gained by analyzing an actual PVC-protein as produced in the plant where the inserted nucleotide sequence suggests it would be minimally modified from a natural plant virus coat protein, e.g., to consider potential post-translational modifications, relative to the reduced burden and cost of analyzing safety based on the deduced amino acid sequence from the insert alone.

Regarding the third alternative presented, EPA requests comment on the rationale that would be used to support expanding this tolerance exemption to cover all PVC-proteins produced by a PVCP-PIP that mediates resistance through PTGS, i.e., that any such protein would meet the conditions of a minimally modified protein as discussed in this document given the necessity for transgene transcript sequence similarity to natural plant virus coat protein sequences in order for PTGS to effectively function. In particular, EPA requests comment on how to reconcile this option with prior advice of the SAP (as discussed in Unit IV.F.).

6. EPA requests comment on whether PVC-proteins that the Agency has reviewed and has determined are minimally modified and therefore are exempt from the requirement of a tolerance under proposed § 174.477(b) should be listed in the CFR as is the current practice for individual tolerance exemptions associated with other types of PIPs. If so, EPA requests comment on whether the listing should indicate the specific modifications of the reviewed proteins, given that each determination would apply only to proteins with those modifications. EPA is aware that in the past, developers have found such listings to be useful for international trade reasons, as governments rely on EPA tolerances to support import decisions.

XII. References

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B. Additional Information

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 in this unit. This official record includes all information physically located in the dockets described in the following paragraphs, as well as any documents that are referenced in the documents in the dockets.

1. 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).

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).

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).

4. 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).

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).

6. 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).

7. 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).

8. 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).

9. 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).

10. 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).

11. The docket identified by the docket control number OPP-300368B 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).

12. The docket identified by the docket control number OPP–300371B 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).

13. 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).

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

15. The docket identified by the docket ID number EPA–HQ–OPP–2006–0642 for the companion document entitled ''Exemption under the Federal Insecticide, Fungicide, and Rodenticide Act for Certain Plant-Incorporated Protectants Derived from Plant Viral Coat Protein Gene(s) (PVCP-PIPs)'' (FRL–8100–7) published elsewhere in this issue of the **Federal Register**.

16. The docket identified by the docket ID number EPA–HQ–OPP–2006–0643 for this document (FRL–8100–5).

Also included in the complete official public record are:

- Public comments submitted in response to the proposals and supplemental documents cited in the above paragraphs.
- Reports of all meetings of the Biotechnology Science Advisory Committee and the FIFRA Scientific Advisory Panel pertaining to the development of this final rule.
- Support documents and reports.
- 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).
- Published literature that is cited in this document.

XIII. Statutory and Executive Order Reviews

This proposed rule would establish an exemption from therequirement of a tolerance under section 408 of FFDCA. The Officeof Management and Budget (OMB) has exempted these types of actionsfrom review under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993). Because this proposed rule has been exempted from review under Executive Order 12866, this proposal is not subject to Executive Order 13211, *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997). This proposed rule does not contain any new information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 et seq., nor does it require any special considerations under Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994). This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA) (15 U.S.C. 272 note). Pursuant to the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 et seq.), the Agency previously assessed whether establishing tolerances, exemptions from tolerances, raising tolerance levels or expanding exemptions might adversely impact small entities and concluded, as a general matter, that there is no adverse economic impact associated with tolerance actions. The factual basis for the Agency's generic certification for tolerance actions published on May 4, 1981 (46 FR 24950). Since this proposed rule will not have an adverse economic impact, EPA hereby certifies under section 605(b) of the RFA that this action will not have a significant adverse economic impact on a substantial number of small entities. Tolerance actions, such as this proposed exemption, directly regulates growers, food processors, food handlers and food retailers, not States or tribes. Tolerance actions do not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000) do not apply to this rule. In addition, this rule does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104–4).

As with all aspects of its proposal, EPA invites your comments on these determinations.

List of Subjects in 40 CFR Part 174

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Plants, Reporting and recordkeeping requirements.

Dated: April 9, 2007.

Stephen L. Johnson,

Administrator.

Therefore, it is proposed that 40 CFR part 174 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 adding § 174.477 to read as follows:

§ 174.477 Plant virus coat protein portion of a PVCP-PIP (PVC-protein); exemption from the requirement of a tolerance.

(a) Residues of a PVC-protein from a PVCP-PIP are exempt from the requirement of a tolerance if the encoded PVC-protein is virtually unmodified when compared to an entire unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part.

(b) When the genetic material that encodes the pesticidal substance or leads to the production of the pesticidal substance has been modified (e.g., through internal deletions, addition of nucleotides from other virus coat protein genes, or substitutions leading to amino acid changes), residues of the PVC-protein may be exempt if the Agency determines, after review, that the encoded PVC-protein has been

minimally modified when compared to an entire unmodified coat protein from a virus that naturally infects plants that humans consume *in toto* or in part.

(c) Agency determinations made under paragraph (b) of this section may be made in response to a petition submitted in accordance with the provisions of 40 CFR part 177 or on the Agency's own initiative.

[FR Doc. E7–7296 Filed 4–17–07; 8:45 am]

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