Indian Tribal Governments (63 FR 27655, May 19, 1998), do not apply to this rule. Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000), which took effect on January 6, 2001, revokes Executive Order 13084 as of that date. EPA developed this rulemaking, however, during the period when Executive Order 13084 was in effect; thus, EPA addressed tribal considerations under Executive Order 13084. For the same reasons stated for Executive Order 13084, the requirements of Executive Order 13175 do not apply to this rule either. For the same reasons, this rule does not have any substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999). This rule directly regulates growers, food processors, food handlers and food retailers, not States. This action does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4).

Pursuant to section 605(b) of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), the Agency hereby certifies that this final rule will not have a significant economic impact on a substantial number of small entities. The Agency's determination is based on the fact that an exemption from the requirement of a tolerance under FFDCA section 408, such as that contained in this rule, will not adversely affect any small businesses. Additional information about the Agency's determination may be found in the small entity impact analysis prepared as part of the economic analysis for the FIFRA rulemaking, which is available in the public version of the official record (Ref. 25). The Agency has also 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 these actions. See 46 FR 24950, May 4, 1981.

This rule is not subject to Executive Order 13211, entitled *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001), because this action is not expected to affect energy supply, distribution, or use.

XII. Submission to Congress and the Comptroller General

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, as added by the Small Business Regulatory Enforcement Fairness Act of 1996, generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of this final rule in the **Federal Register**. This final rule is not a ''major rule'' as defined by 5 U.S.C. 804(2).

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: July 12, 2001.

Christine T. Whitman,

Administrator.

Therefore, 40 CFR chapter I is amended as follows:

PART 174—[AMENDED]

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

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

2. Section 174.475 is added to subpart W to read as follows:

§ 174.475 Nucleic acids that are part of a plant-incorporated protectant; exemption from the requirement of a tolerance.

Residues of nucleic acids that are part of a plant-incorporated protectant are exempt from the requirement of a tolerance.

[FR Doc. 01–17982 Filed 7–16–01; 11:45 am]

BILLING CODE 6560–50–S

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[OPP–300368B; FRL–6057–6]

RIN 2070–AC02

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)

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: The substances plants produce for protection against pests, and the genetic material necessary to produce these substances, are pesticides under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), if humans intend to use these substances for ''preventing, destroying, repelling or mitigating any pest.'' These substances, produced and used in living plants, along with the genetic material necessary to produce them, are also ''pesticide chemical residues'' under the Federal Food, Drug, and Cosmetic Act (FFDCA). EPA calls these substances, along with the genetic material necessary to produce them, plant-incorporated protectants. In this final rule, EPA exempts from the FFDCA section 408 requirement of a tolerance, residues of the pesticidal substance portion and residues of any inert ingredient of any plant-incorporated protectant derived through conventional breeding from a plant sexually compatible with the recipient food plant. EPA has determined that there is a reasonable certainty that no harm will result from aggregate exposure to these residues.

DATES: This rule is effective September 17, 2001. Objections and requests for hearings must be received by EPA on or before September 17, 2001.

ADDRESSES: Objections and hearing requests may be submitted by regular mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit II. of the **SUPPLEMENTARY INFORMATION**.

FOR FURTHER INFORMATION CONTACT: By mail: Philip Hutton, Biopesticides and Pollution Prevention Division, Office of Pesticide Programs (7511C), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington DC 20460; telephone number: (703)

308–8260; e-mail address: hutton.phil@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 plant-incorporated protectants. Potentially affected categories and entities may include, but are not limited to:

Categories	NAICS codes	Examples of potentially affected entities
Pesticide manufacturers	32532	Establishments primarily engaged in the formulation and preparation of agricultural and household pest control chemicals
Seed companies	111	Establishments primarily engaged in growing crops, plants, vines, or trees and their seeds
Colleges, universities, and professional schools	611310	Establishments of higher learning which are engaged in development and marketing of plant-incorporated protectants
Establishments involved in research and development in the life sciences	54171	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 above could also be affected. The North American Industrial Classification System (NAIC) 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 part 174 in title 40 of the Code of Federal Regulations (CFR). If you should have any questions regarding the applicability of this action to a particular entity, consult the technical person listed in the **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Additional Information , Including Copies of This Document and Other Related Documents?

1. *Electronically.*You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations,'' ''Regulations and Proposed Rules,'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the**Federal Register** listings at http://www.epa.gov/fedrgstr/. To access information about the EPA's program for biopesticides go directly to the Home Page for the Office of Pesticide Programs at http://www.epa.gov/pesticides/biopesticides.

2. *In person.* The Agency has established an official record for this action under the docket control number OPP–300368B. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as Confidential Business Information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the Public Information and Record Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

C. How Should I Handle CBI that I Want to Submit to the Agency?

Do not submit any information electronically that you consider to be CBI. You may claim information that you submit to EPA in response to this document as CBI by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public version of the official record. Information not marked confidential will be included in the public version of the official record without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person listed under **FOR FURTHER INFORMATION CONTACT.**

II. Objections and Hearing Requests

Under section 408(g) of the FFDCA, as amended by the Food Quality Protection Act (FQPA), any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. The EPA procedural regulations which govern the submission of objections and requests for hearings appear in 40 CFR part 178. Although the procedures in those regulations require some modification to reflect the amendments made to the FFDCA by the FQPA of 1996, EPA will continue to use those procedures, with appropriate adjustments, until the necessary modifications can be made. The new section 408(g) provides essentially the same process for persons to ''object'' to a regulation for an exemption from the requirement of a tolerance issued by EPA under new section 408(d), as was provided in the old FFDCA sections 408 and 409. However, the period for filing objections is now 60 days, rather than 30 days.

A. What Do I Need to Do to File an Objection or Request a Hearing?

You must file your objection or request a hearing on this regulation in accordance with the instructions provided in this unit and in 40 CFR part 178. To ensure proper receipt by EPA,

you must identify docket control number OPP–300368B in the subject line on the first page of your submission. All requests must be in writing, and must be mailed or delivered to the Hearing Clerk on or before September 17, 2001.

1. *Filing the request.* Your objection must specify the specific provisions in the regulation that you object to, and the grounds for the objections (40 CFR 178.25). If a hearing is requested, the objections must include a statement of the factual issues(s) on which a hearing is requested, the requestor's contentions on such issues, and a summary of any evidence relied upon by the objector (40 CFR 178.27). Information submitted in connection with an objection or hearing request may be claimed confidential by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the information that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential will be included in the public version of the official record without prior notice.

Mail your written request to: Office of the Hearing Clerk (1900), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460. You may also deliver your request to the Office of the Hearing Clerk in Rm. C400, Waterside Mall, 401 M St., SW., Washington, DC 20460. The Office of the Hearing Clerk is open from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Office of the Hearing Clerk is (202) 260–4865.

2. *Tolerance fee payment.* If you file an objection or request a hearing, you must also pay the fee prescribed by 40 CFR 180.33(i) or request a waiver of that fee pursuant to 40 CFR 180.33(m). You must mail the fee to: EPA Headquarters Accounting Operations Branch, Office of Pesticide Programs, P.O. Box 360277M, Pittsburgh, PA 15251. Please identify the fee submission by labeling it ''Tolerance Petition Fees.''

EPA is authorized to waive any fee requirement ''when in the judgement of the Administrator such a waiver or refund is equitable and not contrary to the purpose of this subsection.'' For additional information regarding the waiver of these fees, you may contact James Tompkins by phone at (703) 305–5697, by e-mail at tompkins.jim@epa.gov, or by mailing a request for information to Mr. Tompkins at Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460.

If you would like to request a waiver of the tolerance objection fees, you must mail your request for such a waiver to: James Hollins, Information Resources and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460.

3. *Copies for the docket.* In addition to filing an objection or hearing request with the Hearing Clerk as described in Unit II., you should also send a copy of your request to the PIRIB for its inclusion in the official record that is described in Unit I.B.2. Mail your copies, identified by docket control number OPP–300368B, to: Public Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460. In person or by courier, bring a copy to the location of the PIRIB described in Unit I.B.2. You may also send an electronic copy of your request via e-mail to: opp-docket@epa.gov. Please use an ASCII file format and avoid the use of special characters and any form of encryption. Copies of electronic objections and hearing requests will also be accepted on disks in WordPerfect 6.1/8.0 file format or ASCII file format. Do not include any CBI in your electronic copy. You may also submit an electronic copy of your request at many Federal Depository Libraries.

B. When Will the Agency Grant a Request for a Hearing?

A request for a hearing will be granted if the Administrator determines that the material submitted shows the following: There is a genuine and substantial issue of fact; there is a reasonable possibility that available evidence identified by the requestor would, if established resolve one or more of such issues in favor of the requestor, taking into account uncontested claims or facts to the contrary; and resolution of the factual issues(s) in the manner sought by the requestor would be adequate to justify the action requested (40 CFR 178.32).

III. Under What Authority Is EPA Issuing this Final Rule?

This exemption from the requirement of a tolerance is being issued under the authority of section 408(c) of the FFDCA (21 U.S.C. 346a(c)). 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 other 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 the 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 a commodity or food primarily as a result of the metabolism or other degradation of a pesticide chemical'' (21 U.S.C. 321(q)(2)). The 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)). 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'' with certain exceptions (7 U.S.C. 136(t)).

Under FFDCA section 408(c), EPA can establish an exemption from the requirement of a tolerance for a ''pesticide chemical residue'' only if EPA determines that granting such an exemption is ''safe'' (21 U.S.C. 346a(c)(2)(A)(i)). The 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'' (21 U.S.C. 346a(c)(2)(A)(ii)). This includes exposure through drinking water, and residential and other indoor uses, but does not include occupational exposure. In establishing an exemption from the requirement of a tolerance, FFDCA section 408(c) does not authorize EPA to consider potential benefits associated with use of the pesticide chemical in determining whether the pesticide chemical may be exempted.

FFDCA section 408 requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing an exemption 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'' (21 U.S.C. 346a(b)(2)(C)(ii)(I)) and (c)(2)(B)). FFDCA section 408(b)(2)(D) specifies other general factors EPA must consider in establishing an exemption (21 U.S.C. 346a(b)(2)(D)). FFDCA section 408(c)(3) prohibits an exemption unless there is either a practical method for detecting and measuring levels of pesticide chemical residue in or on food or there is no need for such a method, requiring EPA to state the reason for this determination (21 U.S.C. 346a(c)(3)).

IV. Context

A. What Role Does this Exemption Play in EPA's Approach to Plant-Incorporated Protectants?

The substances plants produce for protection against pests are pesticides under the FIFRA definition of pesticide, if humans intend to use these substances for ''preventing, destroying, repelling or mitigating any pest.'' These substances, produced and used in living plants, along with the genetic material necessary to produce them, are designated ''plant-incorporated protectants'' by EPA.

To understand the role this exemption plays in EPA's approach to plant-incorporated protectants, the following two considerations must be understood. First, what constitutes the residues of plant-incorporated protectants derived through conventional breeding from plants sexually compatible with the recipient plant and why EPA is exempting them from the requirement of a tolerance. Second, how this exemption from the FFDCA requirement of a tolerance for residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants relates to the exemption from the FFDCA requirement of a tolerance published elsewhere in this issue of the **Federal Register** for residues of nucleic acids that are part of a plant-incorporated protectant.

1. *What constitutes the residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants and why is EPA exempting them?* In developing its approach to plant-incorporated protectants, EPA took into account the properties of pesticidal and other substances produced and used in plants. In particular, EPA recognized that plants have evolved, and thus naturally possess, various mechanisms to resist pests. The mechanisms of resistance can be varied, including, for example, structural characteristics of the plant, the production of general metabolites that have toxic properties, or the production of specific toxic substances in response to pest attack. In breeding plant varieties, humans have frequently intentionally used these mechanisms to create varieties with varying abilities to prevent, destroy, repel or mitigate pests. Based on human experience in breeding, growing, preparing, and consuming food from such plant varieties and the large and varied information developed through systematic scientific study available in the literature, EPA recognized that residues of many plant-incorporated protectants, in or on food or feed, would qualify for exemption from regulation under FFDCA section 408. (Hereafter, EPA will use the term ''in food'' to represent the concept of ''in or on food or feed'' in this preamble).

For EPA to exempt any residue of a pesticide, including any residue of a plant-incorporated protectant, EPA must find that there is a reasonable certainty that no harm will result from aggregate exposure to the residue, including all anticipated dietary exposures and all other exposures for which there is reliable information. EPA takes this action today with regard to residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants because it has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the residues, including all anticipated dietary exposures and all other exposures for which there is reliable information.

Under FFDCA section 408, the term residue is defined broadly to include residues of the active and inert ingredients of the pesticide itself and residues that are present in the food as a result of the metabolism or other degradation of the pesticide (21 U.S.C. 321(q)). For plant-incorporated protectants derived through conventional breeding from sexually compatible plants, EPA anticipates the residues will consist of the pesticidal substance and the genetic material necessary for production of the pesticidal substance, and any substance that might function as an inert ingredient as defined for plant-incorporated protectants (e.g., any selectable marker), and the genetic material necessary for production of the inert ingredient.

This action exempts from the requirement of a tolerance under FFDCA section 408, residues of the pesticidal substance portion of plant-incorporated protectants derived through conventional breeding from plants sexually compatible with the recipient plant, and residues of any inert ingredient introduced through conventional breeding from plants sexually compatible with the recipient plant. For plant-incorporated protectants, the recipient plant is the living plant that receives the genetic material necessary to produce the pesticidal substance and in which the plant-incorporated protectant is intended to be produced and used.

2. *How does this exemption relate to the exemption from the FFDCA requirement of a tolerance for residues of nucleic acids?* This exemption can be paired with EPA's tolerance exemption for residues of nucleic acids that are part of a plant-incorporated protectant, published elsewhere in a companion document in this issue of the **Federal Register**. That exemption applies to residues of the genetic material portion of all plant-incorporated protectants, and, thus, also applies to residues of the genetic material necessary for the production of the pesticidal substance portion of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, and the residues of the genetic material necessary for the production of any inert ingredient introduced through conventional breeding from plants sexually compatible with the recipient plant. Because of these actions, all residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants are exempt from FFDCA section 408 requirements.

B. Does this Final Rule Have Any Relevance to Other Types of Pesticides?

Nonviable plant tissues, organs or parts that are used as pesticides, will not be covered by this exemption. Residues of such pesticides are subject to the regulations found in 40 CFR parts 177 through 180 rather than 40 CFR part 174. An example of this type of pesticide would be the powder, produced by drying and grinding cayenne pepper, dusted on plants to protect them from pests.

Residues of substances that are isolated from a plant's tissues and then applied to plants and/or to food for pest control will not be covered by this exemption. Residues of these types of pesticides in formulations such as those for foliar application are subject to regulations found in 40 CFR parts 177 through 180 rather than 40 CFR part 174. An example of this type of pesticide would be pyrethrum isolated from chrysanthemum plants, formulated with other ingredients for foliar application, and sprayed onto other plants for pest control.

Residues of substances that are synthesized will not be covered by this exemption. Residues of such pesticides are subject to regulations found in 40 CFR parts 177 through 180 rather than 40 CFR part 174. An example of this type of pesticide is the herbicide, atrazine.

C. What Is the History of this Final Rule?

This final rule is an additional step in fully implementing the ''Coordinated Framework for Regulation of Biotechnology'' of the United States of America which was published in the **Federal Register** by the Office of Science and Technology Policy (OSTP) on June 26, 1986 (51 FR 23302).

EPA sponsored, or co-sponsored with other Federal agencies, three conferences dealing with plant related issues: On October 19–21, 1987, a meeting on''Genetically Engineered Plants: Regulatory Considerations'' at Cornell University, Ithaca, New York; on September 8–9, 1988, a ''Transgenic Plant Conference'' in Annapolis, Maryland; on November 6–7, 1990, a conference on ''Pesticidal Transgenic Plants: Product Development, Risk Assessment, and Data Needs'' in Annapolis, Maryland. Information from these conferences has been incorporated as appropriate in development of this final rule.

In developing its approach to plant-incorporated protectants, EPA requested the advice of two scientific advisory groups at three meetings. On December 18, 1992, pursuant to section 25 of FIFRA, a subpanel of the FIFRA Scientific Advisory Panel (SAP) was convened to review a draft policy on plant-pesticides (now called plant-incorporated protectants) and to respond to a series of questions posed by the Agency, primarily on 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 plant-pesticides under FFDCA. On January 21, 1994, a joint meeting of the subpanel of the SAP and the BSAC subcommittee was held and EPA asked advice on approaches to plant-pesticides under both FIFRA and FFDCA. Advice from these scientific advisory groups was considered in finalizing this rule.

EPA published in the November 23, 1994, **Federal Register** a package of five separate documents (59 FR 60496, 60519, 60535, 60542, 60545) (FRL–4755–2, FRL–4755–3, FRL–4755–4, FRL–4755–5, FRL–4755–8) which described EPA's policy and proposals for plant-pesticides under FIFRA and FFDCA. Included in that package was a proposal to exempt from the FFDCA requirement of a tolerance, residues of the pesticidal substance portion of plant-pesticides derived from closely related plants.

On July 22, 1996, EPA published a supplemental document in the **Federal Register** (61 FR 27891) (FRL–5387–4) on one aspect of its November 23, 1994, **Federal Register** documents; i.e., how the concept of inert ingredient related to plant-pesticides.

In August of 1996, Congress enacted the FQPA which amended the FFDCA and FIFRA. On May 16, 1997, EPA published in the **Federal Register** a supplemental document (62 FR 27132) (FRL–5717–2) to provide the public with an opportunity to comment on EPA's analysis of how certain FQPA amendments to the FFDCA and FIFRA apply to the proposed tolerance exemption for pesticide chemical residues derived from closely related plants.

On April 23, 1999, EPA published a supplemental document (64 FR 19958) (FRL–6077–6) in the **Federal Register** soliciting comment on whether to change the name of this type of pesticide.

The documents and the reports of the meetings described above are available in the record for the rulemaking for plant-incorporated protectants as described in Unit X.

V. What are the Key Features of the Proposed Exemption?

The development of this exemption consists of a proposed rule which appeared in the November 23, 1994, **Federal Register** (59 FR 60535), and two supplemental documents; one document that appeared on July 22, 1996, in the **Federal Register** (61 FR 37891), and a second that appeared in the May 16, 1997, **Federal Register** (62 FR 27132).

A. November 23, 1994, **Federal Register** *Proposed Rule*

In the 1994 **Federal Register** document (59 FR 60535, November 23, 1994), EPA proposed to exempt residues of a category of plant-pesticides it believed would qualify for an exemption. The proposed exemption was based upon the premise that new dietary exposures would not likely arise for these residues if the genetic material leading to the production of the pesticide chemical residues is derived from a plant that is closely related to the recipient plant; i.e., if the plant that is the donor of the genetic material is closely related to the plant receiving the genetic material.

In the 1994 **Federal Register** document, EPA presented two options for describing a standard based on the relatedness of plants. Option 1, the Agency's preferred option proposed at 40 CFR 180.1137(a), used sexual compatibility as a measure of relatedness between plants. Under this option, residues of a pesticidal substance produced in a living plant as part of a plant-pesticide would be exempt from the requirement of a tolerance if the genetic material that encodes for the pesticidal substance or leads to the production of the pesticidal substance is derived from a plant that is sexually compatible with the recipient plant and has never been derived from a source that is not sexually compatible with the recipient plant.

Option 2 would utilize the rank of genus as the taxonomic standard for describing closely related plants, as well as sexual compatibility. This option would exempt residues of a pesticidal substance derived from a plant classified in the same genus as the recipient plant, as well as residues of a pesticidal substance derived from a plant sexually compatible with the recipient plant. Under both Options 1 and 2, residues of the pesticidal substance derived from plants sexually compatible with the recipient plant would be exempt, even if the source and recipient plants are classified in different genera.

EPA proposed that ''sexually compatible,'' when referring to plants, would mean ''capable of forming a viable zygote through the fusion of two gametes, including the use of bridging and/or wide crosses between plants.'' EPA proposed that ''bridging crosses between plants'' would mean the ''utilization of an intermediate plant in a cross between the intermediate plant and the first plant, in order to cross the plant resulting from that zygote with a third plant that would not otherwise be able to produce viable zygotes from the fusion of its gametes with those of the first plant. The result of the bridging cross is the mixing of the first and third plant through the formation of an intermediate zygote.'' EPA proposed that ''wide crosses between plants'' would mean ''to facilitate the formation of viable zygotes through the use of surgical alteration of the plant pistil, bud pollination, mentor pollen, immunosuppression, *in vitro* fertilization, pre-pollination and post-pollination hormone treatments, manipulation of chromosome numbers, embryo culture, or ovary and ovule cultures or any other technique that the Administrator determines meets this definition.''

Neither of the options was intended to exempt residues of a pesticidal substance that is significantly different functionally from the pesticidal substance as it occurs in the source plant.

The Agency also requested comment on the utility of an exemption criterion based on the process (e.g., rDNA) used to introduce the plant-incorporated protectant into a plant (59 FR at 60514, 60540, 60541). This approach was discussed by the SAP Subpanel and BSAC Subcommittee at the joint meeting of these scientific advisory groups held on January 21, 1994. In this approach, residues of plant-incorporated protectants developed through techniques other than those of modern biotechnology would be exempted, e.g., residues of those plant-incorporated protectants developed through conventional plant breeding would be exempted. Residues of those plant-incorporated protectants that were not exempted could subsequently be considered for exemption on the basis of risk potential.

The joint Subcommittee/Subpanel report justified such an approach on the following three considerations. First, the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules established a precedent that has worked well. Second, although new techniques, such as rDNA are more precise than conventional plant breeding, it is possible to make with rDNA novel genetic modifications never before possible. The novel combinations possible with modern genetic techniques create uncertainties about how the gene will function and how its products may affect the plant's phenotype and its impact upon the environment and human health. Third, establishing rDNA methodologies as a criterion for oversight may give the public more confidence that risk potential is being evaluated. As a result, approved products may move to the marketplace more easily (Ref. 6).

B. What Issues Were Discussed in the Supplemental Documents?

Subsequent to publication of the November 23, 1994 **Federal Register** document (59 FR 60535), EPA published two supplemental documents directly relevant to this exemption: one on July 22, 1996 (61 FR 37891), and another on May 16, 1997 (62 FR 27132).

1. *July 22, 1996.* The July 22, 1996, supplemental document (61 FR 37891) discussed how the concept of inert ingredient related to plant-pesticides.

2. *May 16, 1997.* In August of 1996, the FFDCA and FIFRA were amended by the FQPA. On May 16, 1997, EPA published in the **Federal Register**, a supplemental document (62 FR 27132) to provide the public with an opportunity to comment on EPA's analysis of how certain FQPA amendments to the FFDCA and FIFRA affect this proposed exemption.

EPA stated in the May 16, 1997, supplemental document its belief that most of the substantive factors the FFDCA now requires EPA to consider when evaluating pesticide residues were considered when the Agency proposed the exemption in 1994. EPA, thus, in the supplemental document, specifically sought comment only on its evaluation of the requirements imposed by FQPA that the Agency had not addressed in the proposed rule. EPA sought comment on the following five considerations. First, whether there are substances, outside of the food supply, sharing a common mechanism of toxicity with residues of pesticidal substances derived from sexually compatible plants. Commenters were asked to submit information on the cumulative effects of such substances and the pesticidal substances that were the subject of the proposed exemption (59 FR 60535). Second, whether there are substances, outside of the food supply, related via a common mechanism of toxicity to such residues to which humans might be exposed through non-occupational routes of exposure. Commenters were asked to describe routes through which such exposure might occur, including exposure to major identifiable subgroups of human populations (e.g., infants and children). Commenters were requested, if such routes were identified, to provide information on the nature and levels of expected exposures. Comments were also sought on these two issues with regard to Option 2, the alternative option for describing closely related plants (described in Unit V.A.). Third, commenters who possess information on substances occurring in food from plants that may have estrogenic effects and may be used as plant-incorporated protectants were requested to send such information to EPA. Fourth, EPA described in greater detail the rationale supporting the statement made in the 1994 **Federal Register** document (59 FR at 60513) that ''plant-pesticides are likely to present a limited exposure of pesticidal substances to humans. In most cases, the predominant, if not the only, route of exposure will be dietary. Significant respiratory and dermal exposures will be unlikely.'' No comments were received on this statement during the first comment period for the proposed rule. The public was given the opportunity to comment on EPA's more detailed rationale supporting the statement. Fifth, EPA also described in greater detail how the rationale presented in the 1994 **Federal Register** document (59 FR at 60538) concerning the safety for human consumption of food from plants that meet the sexually compatible standard applies to infants and children. The public was given the opportunity to comment on the more detailed rationale specifically addressing infants and children as part of the larger human population.

VI. What are the Key Features of this Final Rule?

In this final rule, EPA exempts residues of the pesticidal substance and inert ingredient portion of plant-incorporated protectants derived through conventional breeding from plants sexually compatible with the recipient plant. The following language is added to 40 CFR 174.479:

> Residues of a pesticidal substance that is part of a plant-incorporated protectant from a sexually compatible plant are exempt from the requirement of a tolerance if all the following conditions are met:
>
> (a) The genetic material that encodes for the pesticidal substance or leads to the production of the pesticidal substance is from a plant that is sexually compatible with the recipient food plant.
>
> (b) The genetic material has never been derived from a source that is not sexually compatible with the recipient food plant.
>
> (c) The residues of the pesticidal substance are not present in food from the plant at levels that are injurious or deleterious to human health.

Pertinent associated definitions in 40 CFR 174.3 are discussed in greater detail in a companion document published elsewhere in this issue of the **Federal Register** on FIFRA regulations for plant-incorporated protectants.

In this final rule, plant means an organism classified using the 5-kingdom classification system of Whittaker (Ref. 1) in the kingdom, Plantae. Therefore, the term ''plant'' includes, but is not limited to, bryophytes such as mosses, pteridophytes such as ferns, gymnosperms such as conifers, and angiosperms such as most major crop plants.

Also included in the regulatory text at § 174.485, subpart X, is an exemption for residues of inert ingredients in plants derived through conventional breeding from sexually compatible plants.

VII. How Do the Proposed Rule and Final Rule Differ?

This exemption from the requirement of a tolerance is adopted with several

changes from the proposed rule published in 1994 (59 FR 60535, November 23, 1994). EPA has changed the name of this type of pesticide from ''plant-pesticide'' to ''plant-incorporated protectant'' as described in the companion document on FIFRA regulations for plant-incorporated protectants published elsewhere in this issue of the **Federal Register**. EPA exempts at this time only a subgroup of the category it proposed to exempt in 1994: Residues of pesticidal substances and inert ingredients derived through conventional breeding from plants sexually compatible with the recipient plant. In a companion document published elsewhere in this issue of the **Federal Register**, EPA solicits additional comment on alternative options for the plant-incorporated protectants derived through modern biotechnology, e.g., recombinant DNA techniques, from plants sexually compatible with the recipient plant.

In response to concerns expressed in comments and to make EPA's approach more consistent with the policy of the Food and Drug Administration (FDA), EPA has added a condition to the exemption that addresses levels of substances that are injurious or deleterious to human health in food from plants in sexually compatible populations. A few other modifications have been made to the text of the exemptions, for purposes of clarification. A discussion of modifications to other relevant definitions, including an analysis of comments on those definitions, can be found in a companion document published elsewhere in this issue of the **Federal Register** on FIFRA regulations for plant-incorporated protectants. Discussion of all modifications can be found in the documents summarizing public comments and EPA responses on issues associated with plant-incorporated protectants (Ref. 2) located in the record for this rule as described in Unit X.

When EPA proposed the exemption in 1994 at 40 CFR 180.1137(a), it also stated its intention (59 FR at 60520) to establish a new 40 CFR part 174 specifically for plant-incorporated. This new 40 CFR part 174 is being established in a companion document published elsewhere in this issue of the **Federal Register**. EPA adds this tolerance exemption to 40 CFR 174.479, subpart W, rather than adding it to 40 CFR part 180 as proposed.

VIII. Discussion of Final Rule and Public Comments

In this unit, EPA discusses the final rule and summarizes the comments it received on the November 23, 1994 proposed rule and the May 16, 1997 supplemental document. EPA reviewed and considered all comments received on the proposed rule and supplemental document and prepared detailed responses to these comments. These responses can be found at appropriate points in this preamble and in the Agency's summary of public comments and EPA's response on issues associated with plant-incorporated protectants (Ref. 2).

A. From Whom Did EPA Receive Comments?

In response to the package of documents published in the **Federal Register** in 1994, EPA received letters from industry, academia, professional and trade associations, government agencies, state regulatory authorities, public interest groups and private citizens. Some of the commenters sent separate letters for each of the five dockets associated with the 1994 **Federal Register** documents. Other commenters sent a single letter addressing all five dockets. EPA received comments on the July 22, 1996, supplemental document, and on the May 16, 1997, supplemental document, which provided the public an opportunity to comment on EPA's analysis of how certain amendments to the FFDCA and FIFRA by FQPA affected this proposed exemption. Copies of all comments received are available in the record for this rule as described in Unit X.

B. Exemption of Residues of Plant-Incorporated Protectants Derived Through Conventional Breeding from Sexually Compatible Plants

On November 23, 1994 (59 FR 60535), EPA proposed to exempt from the FFDCA requirement of a tolerance, all residues of a category of plant-incorporated protectants based on the premise that new dietary exposures would be unlikely if the genetic material leading to the production of the plant-incorporated protectant is derived from a plant closely related to the recipient plant. EPA offered two options for defining plant-incorporated protectants derived from plants closely related to the recipient plant. The options were somewhat different approaches to describing a high degree of relatedness between the genetic donor and the recipient plant. Neither of the options was based on the process by which a plant-incorporated protectant was introduced into the recipient plant. Option 1, based upon sexual compatibility, was EPA's preferred option (59 FR 60542). Option 2, used taxonomy (genus) in conjunction with sexual compatibility to define closely related plants. The Agency also requested comment on the utility of an exemption criterion based on the process (e.g., rDNA) used to introduce the plant-incorporated protectant into a plant (59 at FR 60514, 60540, 60541).

During the comment period for the 1994 proposed rule, EPA received 19 comments addressing the options for describing pesticidal substances derived from closely related plants. Nine of these comments supported Option 1 and generally agreed that the sexual compatibility standard is reasonable and adequately addresses food safety issues. Three comments favored Option 2, with one of these comments arguing that species belonging to the same genus are closely related and thus have a high degree of biochemical similarity even though they may not be sexually compatible. The commenter also cited the history of safe use of foods from plant varieties developed through plant breeding. EPA also received comments expressing serious reservations about using, for this exemption, a taxonomic standard for describing closely related plants (i.e., Option 2), because taxonomic categories, and the relationship of a given plant species to a given taxon, may be transient since taxonomic categories may change as information accrues. Others expressed concern that dietary risk may be presented by such a standard.

EPA received 37 comments on the use of the process by which the genetic material is introduced into the plant as an exemption criterion. Twenty of these comments supported an approach based on process, i.e., that those plant-incorporated protectants introduced by rDNA would be regulated. The arguments advanced by these commenters can be represented by the comment that:

> Genetic engineering (particularly recombinant DNA [rDNA] methodologies), represents a fundamental technical advance over traditional plant breeding in the ability to manipulate plants genetically. Genes which code for production of plant-pesticides can be readily turned 'on' or 'off' to dramatically increase the existing levels of plant-pesticides within plants, turning plants into pesticide factories and delivery systems. . . . given the fact that rDNA technologies represent such a fundamental technical advance over plant breeding, and given that plant-pesticides are by their very nature toxic substances, all plant-pesticides produced via rDNA methodologies should undergo some form of review under both FIFRA and FFDCA . . . (Ref. 3).

Several letters described quantitative changes in the levels of plant-incorporated protectants as specific

instances in which the commenter believed risk would be better addressed by an approach based on process. One of these commenters did not agree with EPA's analysis that levels of the plant-incorporated protectants (and thus of their residues) are likely to fall, in the vast majority of cases, within ranges currently found in safely consumed food from plants. Another of these commenters urged EPA to modify the proposed exemption so that the Agency would be notified if levels of pesticidal substances are ''deliberately increased through the introduction or modification of promoters or other noncoding regulatory sequences or there is reason to believe that levels of a plant-pesticide in food or feed derived from a particular crop will be increased by an order of magnitude or more'' (Ref. 3).

In response to the May 16, 1997, supplemental document, EPA received six comments. Five comments supported exemption of residues of plant-incorporated protectants derived from sexually compatible plants, with four comments addressing specific questions posed by EPA. One commenter, however, opposed any exemption that did not take into account quantitative changes in the levels of these residues, stating that ''current knowledge is certainly inadequate to sanction greatly increased levels of these substances'' in food (Ref. 4).

Some comments urging regulation based on whether rDNA had been used to introduced the plant-incorporated protectant, supported exempting conventional breeding. One commenter, for example, stated ''that a long record of experience with the products of natural evolution and traditional breeding shows that they typically do not present new dietary exposures and should be exempt from tolerance requirements'' (Ref. 5).

Based on the advice of the BSAC and SAP at the joint meeting held January 21, 1994, and the comments received in response to the November 23, 1994 **Federal Register** document, EPA has determined that it is appropriate at this time to exempt from the FFDCA tolerance requirement those residues of the pesticidal substance portion of plant-incorporated protectants, as well as any inert ingredients derived through conventional breeding from plants sexually compatible with the recipient plant. In a companion document published elsewhere in this issue of the **Federal Register**, EPA solicits public comment on alternative options for the category of residues of pesticidal substances derived through the techniques of modern biotechnology, e.g., recombinant DNA, from plants sexually compatible with the recipient plant. The Agency is considering these options in response to public comment on its earlier proposals. One of these options would establish notification procedures, and as the public has not had an opportunity to comment on either the procedures themselves, or the criteria on which EPA would base its regulatory decisions, the Agency believes it would be appropriate to seek additional public comment prior to adopting a particular option. In addition, as these alternatives would distinguish between categories of residues of plant-incorporated protectants based solely on the processes by which they are derived, the public will also have an opportunity to present comments on whether this is an appropriate distinction for regulatory purposes.

C. What is the Language of the Exemption?

In this final rule, EPA is, at 40 CFR 174.479, exempting only a subgroup of the category of residues it proposed to exempt in 1994, pesticide chemical residues derived through conventional breeding from plants sexually compatible with the recipient plant. EPA discusses the language of the exemption as it applies to this subcategory.

1. *Why is sexual compatibility an appropriate standard?* EPA believes that sexual compatibility is an appropriate standard because sexually compatible plants share a common pool of genetic material, even though there may be some variability among plants in sexually compatible populations. Sexual compatibility, the ability to produce viable offspring, is only possible in nature for plants that possess many traits in common. Traits, and the genetic material encoding them, can be passed through sexually compatible plant populations by hybridization, and the mixing of genetic material that occurs through this process of mating tends to a situation where the members of sexually compatible population have similar traits and similar genetic material. This is particularly true with crop plants where generations of selection and breeding have tended to increase the homogeneity of traits used to produce agriculturally important cultivars. Sexual compatibility thus presents a natural grouping of plants which can be readily described and used as a regulatory standard, and about which a large amount of information exists in the scientific literature. This information can be used in assessing risk.

Using sexual compatibility as a standard affords a clear delineation of whether the residues of a plant-incorporated protectant meet the conditions of the exemption. In most cases, whether two plants are sexually compatible is known; thus, testing to determine whether the plants are sexually compatible is not likely to be necessary. If, in rare cases, it is not known whether two plants are sexually compatible, the means of determining sexual compatibility is straightforward and simple. Sexual compatibility is empirically demonstrable. EPA believes that the criterion of sexual compatibility provides a high level of regulatory clarity and the greatest ease of implementation, while at the same time presenting the lowest probability of novel dietary exposure. This standard allows the public, industry, and EPA to easily and readily identify those plant-incorporated protectants that meet the criterion of being derived from plants closely related to the recipient plant.

i. *Why is sexual compatibility limited to conventional breeding?* As explained in a companion document published elsewhere in this issue of the **Federal Register**, EPA is soliciting additional comment on the various options it is considering in response to the significant comments it has received raising issues specific to plant-incorporated protectants derived through genetic engineering. Because none of the comments raised significant issues relative to pesticide chemical residues of plant-incorporated protectants derived through conventional breeding, the Agency is finalizing its proposals with respect to residues of this subgroup of products. In a final rule under FIFRA described elsewhere in a companion document in this issue of the **Federal Register**, EPA includes in the definition of sexually compatible at 40 CFR 174.3 the clause ''through conventional breeding.'' EPA also provides a definition of conventional breeding that equates it to the creation of progeny through either: The union of gametes, i.e., syngamy, brought together through processes such as pollination, including bridging crosses between plants and wide crosses; or vegetative reproduction. Conventional breeding does not include use of any of the following technologies: Recombinant DNA; other techniques wherein the genetic material is extracted from an organism and introduced into the genome of the recipient plant through, for example, micro-injection, macro-injection, micro-encapsulation; or cell fusion. EPA believes that this

definition addresses the recommendation of the SAP/BSAC that ''the Agency define methodologies in a way that clearly delineates to the scientific community and the public what is and is not included in the regulatory scope'' (Ref. 6).

In the 1994 proposed rule (59 FR at 60538) and in the 1997 supplemental document (62 FR at 27135), EPA states that its proposed rule is based on ''experience with the exposure of human populations to crops developed through the breeding process, i.e., crops developed through 50 to 100 years of scientific breeding among sexually compatible plant populations using Mendelian genetics.'' In its 1994 proposed rule, EPA calls this type of breeding, ''traditional breeding'' (see e.g., 59 FR 60519). When the Agency determined that it would exempt a subgroup of residues of the sexually compatible grouping, while allowing additional comment on how the Agency should treat the residues of those plant-incorporated protectants introduced into the plant through the techniques of modern biotechnology, EPA chose to describe the exempt group of residues in the most straightforward manner, as those derived through breeding in sexually compatible populations. Recognizing that many consider the modern techniques of biotechnology as simply an extension of breeding techniques, EPA determined that an adjective was needed to modify the word ''breeding'' to adequately describe the exempt group. Although the Agency used the word ''traditional'' in its 1994 proposed rule, EPA chose the word ''conventional'' to describe this type of breeding in this rule because the SAP/BSAC in the report of their January 21, 1994 joint meeting used the adjective ''conventional'' in its advice to EPA (Ref. 6), and the word ''conventional'' might more readily connote techniques such as wide crosses.

ii. *Why is conventional breeding described by processes such as pollination and vegetative reproduction?* One comment received on the 1994 proposed rule suggested that there is ambiguity in the proposed regulatory language at 40 CFR 174.5(a) in the November 23, 1994, **Federal Register** document (59 FR 60535). The commenter indicated the perceived ambiguity could lead to questions about whether plant-incorporated protectants that are ''native'' to a food crop would meet the criteria of exemption.

Because of the use of the word ''food'' in the comment, it was not clear whether the comment is directed toward EPA's proposed exemption under FIFRA or that under the FFDCA for residues of plant-incorporated protectants derived from plants sexually compatible with the recipient plant. EPA assumes this comment is directed at both exemptions, and that the commenter's suggestion is that EPA ensure that the regulatory language exempts from the FFDCA tolerance requirements, residues of those plant-incorporated protectants that normally occur in a plant (i.e., are ''native'' to the plant) and will be used in that plant. For example, if corn normally produced a plant-incorporated protectant, the regulatory text should be clear that the residues of the plant-incorporated protectant would be exempt when produced and used in corn. EPA believes inclusion of the word ''pollination'' as an example of a process leading to syngamy in the definition of conventional breeding addresses this concern. EPA believes the word ''pollination'' is appropriate because pollination is the process through which traditional breeding occurs (see e.g., 59 FR 60537) (Ref. 7). Inclusion of the word ''pollination'' in the definition emphasizes that plant-incorporated protectants that occur naturally in a plant growing from a viable zygote that arises by the mating in conventional breeding of one corn variety with another, or the mating of a corn plant with a corn plant of the same variety, are exempt.

EPA recognizes that this same concern also applies to plant-incorporated protectants in plants that are propagated vegetatively. EPA believes inclusion of the phrase ''vegetative reproduction'' in the definition of conventional breeding addresses this concern. The language of the exemption for pesticide chemical residues derived through conventional breeding from sexually compatible plants specifically exempts residues in plants reproduced vegetatively. For example, residues of a plant-incorporated protectant in a plant propagated only vegetatively, (e.g., bananas), are exempt. Also exempt are residues of a plant-incorporated protectant in a plant propagated primarily vegetatively (e.g., potatoes), as long as, under conditions of reproduction through hybridization, the plant donating the genetic material is sexually compatible with the recipient plant as defined in at 40 CFR 174.3, and the other conditions described at 40 CFR 174.479 are met. Inclusion of this term in the definition of conventional breeding reflects EPA's statement in the 1994 proposed rule (59 FR 60524) on the status of crop plant varieties propagated vegetatively.

iii. *Will wide and bridging crosses be part of the definition of conventional breeding?* In the final rule under FIFRA described elsewhere in a companion document in this issue of the **Federal Register**, EPA defines ''conventional breeding'' to include wide and bridging crosses. These definitions are also important to this FFDCA tolerance exemption, and thus, EPA discusses them in this preamble.

In the final rule, wide crosses include use of surgical alteration of the plant pistil, bud pollination, mentor pollen, immunosuppressants, *in vitro* fertilization, pre-pollination and post-pollination hormone treatments, manipulation of chromosome numbers, embryo culture or ovary and ovule cultures. Generations of artificial hybridizations through these techniques have taken place in the well-established practices of plant breeding (Ref. 8). Wide crosses, have been in the past and are currently, commonly used to expand the plant gene pool for varietal improvement, and a history of safe use has been associated with plant varieties developed through the use of wide cross techniques (Ref. 8). A fairly high degree of relatedness between the parental plants is indicated when a wide cross produces a viable zygote. This high degree of relatedness indicates a low probability of new exposures. Agricultural plants safely consumed as food have been developed in the past 100 years utilizing wide crosses in the breeding process.

The definition of ''bridging crosses between plants'' is intended to convey the concept that an intermediate plants could be used in a cross to move traits from a source plant into a desired recipient plant. The intermediate plant can form viable zygotes with both the source and recipient plants, whereas the source and recipient plant cannot form viable zygotes. The intermediate plant serves as a bridge for gene flow between the two incompatible plants. The result of the bridging cross is the mixing of genetic material of the first and third plant through the formation of an intermediate zygote. No comments were received on the proposed definition of bridging crosses between plants, also part of the definition of conventional breeding for sexually compatible. EPA is adopting this definition as proposed.

iv. *Will cell or protoplast fusion be part of the definition of wide crosses?* EPA received one comment suggesting that protoplast fusion should be included in the definition of wide crosses between plants. That request was made in the context of the proposal to exempt plant-incorporated protectants derived from plants sexually

compatible with the recipient plant from FIFRA requirements, but as the definition of wide crosses is also relevant for this FFDCA exemption, EPA will discuss that comment in this preamble.

In the technique of protoplast fusion, protoplasts are made in the laboratory through the removal of the cell walls of somatic cells. A somatic cell is a type of cell that forms plant vegetative tissues and organs and is distinguished from a germ cell which undergoes meiosis to produce reproductive tissues (e.g., pollen and egg cells). In the technique of protoplast fusion, protoplast are made from the somatic tissues of two different plants. The membranes of the different protoplasts are then fused together mechanically through processes such as treatment with polyethylene glycol, producing a hybrid somatic cell with a genetic make-up resulting from the combination and sorting of the two plant genomes. The somatic hybrid cell is then grown on specialized media into a mature plant.

In support of the request, the commenter argued that the hybridization of somatic cells (i.e., protoplast fusion) has a history of use to artificially induce sexual compatibility. The commenter argued that movement of genetic material by this means has historically been considered safe.

EPA did not, in its 1994 proposed rule include protoplast fusion in the definition of wide crosses between plants, nor did it perform an analysis of the potential for new dietary exposures when protoplast fusion is used to perform wide crosses between plants. The commenter did not provide such information in response to the 1994 proposed rule nor the 1997 supplemental document. EPA does not believe information currently in the record supports inclusion of protoplast fusion in the definition of wide crosses. Therefore, EPA does not include protoplast fusion in the definition of wide crosses and specifically excludes cell fusion from the definition of conventional breeding. However, EPA requests comment on whether protoplast fusion should be included in the definition of wide crosses in a supplemental document published elsewhere in this issue of the **Federal Register**. EPA would welcome submission of information on protoplast fusion. If the Agency obtains sufficient information demonstrating a low probability of risk, EPA may initiate notice-and-comment rulemaking under FIFRA section 25(b) and FFDCA section 408 to include protoplast fusion in the definition of wide crosses between plants.

v. *''Recombinant DNA'' and genetic material ''extracted from an organism and introduced into the genome of the recipient plant.''* As explained previously, EPA restricted this exemption to conventionally bred plant-incorporated protectants while the Agency solicits additional comment on the alternatives it is considering in response to the comments received on the 1994 proposal. Thus, in order to fully describe which plant-incorporated protectants are exempt under this exemption, EPA includes limiting phrases. EPA in the 1994 **Federal Register** document (59 FR 60541, November 23, 1994) discussion of the advice of the joint SAP/BSAC at the January 21, 1994 meeting on the use of a process-based criterion to define a category of plant-incorporated protectants that would be subject to review, stated that the Agency would define such a process-based criterion in the following way: ''The genetic material that encodes for the pesticidal substance or leads to the production of the pesticidal substance is extracted from an organism and introduced into the genome of the recipient plant or is synthesized *in vitro* and introduced into the genome of the recipient plant.'' EPA in this action uses the language it put forth in the 1994 **Federal Register** to fashion two of the exclusions from the conventional breeding definition at 40 CFR 174.3. One exclusion is for techniques involving the direct introduction into an organism of genetic material extracted from the source and introduced into a recipient plant. Processes such as micro-injection, macro-injection and micro-encapsulation would be excluded from the conventional breeding definition because they are used to introduce such extracted genetic material into the recipient plant. These processes have been included in the definition as examples to assist in understanding the concept.

The second exclusion from the conventional breeding definition uses the term ''recombinant DNA'' to represent the concept of ''extracted from an organism. . ., synthesized *in vitro* and introduced into the genome of the recipient plant.'' To provide greater technical accuracy, EPA provides a definition at 40 CFR 174.3 for recombinant DNA as follows: ''Recombinant DNA means the genetic material has been manipulated *in vitro* through the use of restriction endonucleases and/or other enzymes that aid in modifying genetic material, and subsequently introduced into the genome of the plant.''

2. *Why is the concept of ''functionally modified from the source'' important and how does the definition of conventional breeding address it?* In the November 23, 1994 **Federal Register** document (59 FR at 60539), EPA explained that in proposing the exemptions the Agency did not intend to exempt residues of a pesticidal substance that is significantly different functionally, from the pesticidal substance as it occurs in the source plant. EPA believed this limitation is appropriate because rearrangements or modifications of the genetic sequence encoding a pesticidal substance made through the use of techniques such as rDNA could, for example, result in a plant-incorporated protectant, and/or residues of such a plant-incorporated protectant, with significantly different functions from the function in the source plant. For example, if the pesticidal substance is an enzyme, it could be modified so that it acts on a different substrate in the recipient plant than it did in the source plant (Refs. 8 and 9). Residues of such a significantly modified pesticidal substance would not necessarily present risks similar to the substance prior to modification, nor would the base of experience on which EPA relies for support of the exemption necessarily be relevant. If the genetic material encoding the pesticidal substance has been modified in such a way that the pesticidal substance functions differently in the recipient plant than it did in the source plant, the analysis performed to determine that there is a reasonable certainty that no harm will result from aggregate exposure to the residues of the plant-incorporated protectant, would not apply.

In this final rule, this concern is addressed by the limitation placed on the definition of sexually compatible. Under this definition, residues of pesticidal substances from sexually compatible plants are only exempt if the genetic material is introduced into the plant through conventional breeding as defined at 40 CFR 174.3. The types of changes discussed above (Refs. 8 and 9) that can be made through modern molecular techniques, are very unlikely to be made through conventional breeding as defined at § 174.3, and residues of plant-incorporated protectants modified through modern molecular techniques are not eligible for today's exemption.

3. *Why is the phrase ''never derived from source not sexually compatible with recipient plant'' important?* EPA discussed the relevance of this phrase to the proposed exemption in the November 23, 1994 **Federal Register**

document (59 FR 60539). The phrase, ''has never been derived from a source that is not sexually compatible with the recipient plant,'' was included in the proposed regulatory text to clearly indicate that pesticide chemical residues of a plant-incorporated protectant would not qualify for the exemption if the genetic material is introduced into a recipient plant from a sexually incompatible source and then subsequently introduced from this recipient plant into other plants sexually compatible with the recipient plant. For example, the exemption does not extend to a situation where the genetic material encoding the *Bacillus thuringiensis* delta endotoxin is introduced into wheat, and the endotoxin-producing wheat is subsequently hybridized with rye using wide cross techniques to produce triticale. The residues of the endotoxin produced in the triticale would not be eligible for the exemption because the genetic material encoding the endotoxin originated from a bacterium, a source that is not sexually compatible with the original recipient plant (wheat in this example).

One commenter suggested that the Agency delete this phrase from the regulatory text and instead include a period of time after which a plant-incorporated protectant would be treated as part of a plant's ''accessible'' gene pool. EPA disagrees and will continue to include this language in the final rule at 40 CFR 174.479. Further, EPA disagrees with the commenter's suggestion that a gene, derived from a phylogenetically distant source and successfully used in a crop, be treated after a period of time as though it had become part of the crop's gene pool (i.e., equivalent to a gene that had evolved in a sexually compatible population of plants). The commenter does not suggest what an appropriate period of time would be nor how this would correlate with the potential for dietary exposures. Without additional information, EPA cannot find that there is a ''reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue'' as required by FFDCA section 408(c).

4. *Why is EPA placing a condition on the exemption limiting the levels of pesticidal substances?* To address concerns raised in comment on its original proposal concerning the possibility that certain substances normally present in plants in sexually compatible populations may in rare circumstances be present in food at levels that are hazardous, EPA is limiting this exemption by requiring that the residues of the pesticidal substance not be present in food from the plant at levels that are injurious or deleterious to human health. EPA is including at 40 CFR 174.479, the following condition to the language of the exemption: ''(c) The residues of the pesticidal substance are not present in food from the plant at levels that are injurious or deleterious to human health.''

If the residues of the plant-incorporated protectant do not meet this criterion, they are not exempt from the requirement of a tolerance, nor would a tolerance have been established for them. A food containing residues of a pesticide may not be moved in interstate commerce without either an appropriate tolerance or an exemption from the requirement of a tolerance. Should such an occurrence be identified, the condition will allow expeditious removal of the offending food from the market. EPA does not believe that such an occurrence will result *a priori* in a reevaluation of the categorical exemption for pesticidal substances derived through conventional breeding from sexually compatible plants under FFDCA section 408 because any problem will likely be associated with a single variety.

Producers who wish to increase the levels of pesticidal substances in plants in sexually compatible populations beyond the ranges of levels generally seen in plant varieties currently on the market and known to produce food safe for consumption are strongly encouraged to consult with EPA to determine whether their plant-incorporated protectant is eligible for the exemption from the requirement of a tolerance, or whether a tolerance, and therefore, a registration is necessary. Based on the record compiled for this rulemaking on the historical safety of food from plants in sexually compatible populations, as described in Unit IX.A. and Unit IX.B.1., EPA believes that such a circumstance, will be extremely unlikely for residues derived through conventional breeding from plants sexually compatible with the recipient plant.

This condition makes EPA's approach to plant-incorporated protectants more consistent with FDA's regulatory approach, and allows the agencies to act more expeditiously in the rare circumstance that a risk associated with higher levels of substances normally part of a plant in a sexually compatible population is identified in food.

This condition, in conjunction with the reporting requirement at 40 CFR 174.71, is conceptually similar to the suggestion of one commenter that the Agency be notified if levels of pesticidal substances are significantly increased. EPA disagrees, however, with the commenter's suggestion that notification be required only when levels of pesticidal substances are increased by 10 fold. There is natural variability in levels of expression in a plant of any substance, including plant-incorporated protectants, influenced by factors such as genetic composition, soil composition, climate and weather. Humans are currently being exposed to variation in the food they consume. The commenter did not provide information to support the suggestion that a 10-fold increase would represent an unacceptable risk, and broad adoption of such a standard would be arbitrary. The variations normally seen in food from plants, such as the 20-fold variation for ascorbic acid in muskmelon depending on variety planted, and the variation in the levels of carotene in carrots which can range from none detectable to 370 mg/100 g tissue depending on the variety (Ref. 8), are greater than the 10-fold increase suggested by comment. Other examples can be offered where the variation falls within a more narrow range, for example, one researcher (Ref. 8) reported that depending on maturity of the fruit, the level of ascorbic acid in tomato can range from 2.7 mg/100 g tissue to 7.6 mg/100 g tissue, a 2.8-fold variation. The conditions on the exemption at § 174.479 and reporting requirement at § 174.71, on the other hand, have no numerical standards. Nevertheless, the Agency believes that the adverse effects reporting requirement will allow the Agency to monitor for any rare instances in which significant increases in levels of plant-incorporated protectants might present a hazard, and that the condition at § 174.479 will allow EPA and FDA to act expeditiously. (The adverse effects reporting requirement is described in a companion document published elsewhere in this issue of the **Federal Register** on FIFRA regulations for plant-incorporated protectants).

The historical safety of the food supply as described by the record EPA has compiled for this exemption, the reporting requirement imposed as a condition of the FIFRA exemption, taken in conjunction with the strong likelihood that manufacturers and companies will choose to consult with EPA rather risk seizure of their food by FDA, cause EPA to believe that the condition placed on the exemption sufficiently address the commenters' concerns.

5. *Why does 40 CFR 174.479 include language limiting the recipient to food plants?* In the preamble to the 1994

proposed rule (see e.g., 59 FR 60537), EPA discussed the premise for this exemption; that ''new dietary exposures would not likely arise for plant-pesticides produced in recipient food plants if the genetic material leading to the production of the pesticidal substance is derived from closely related plants.'' In addition, the BSAC in its report on the July 13, 1993 meeting (Ref. 10) emphasized to the Agency that the focus of an exemption should be on plant-incorporated protectants in food plants. They suggested that ''plant-pesticides in plants commonly consumed by humans as food be exempt as long as the plant's genetic material is derived from related plants within the same family that have contributed traits to the food plant through the mechanism of sexual recombination (including wide crosses and embryo rescue)'' (59 FR 60540). In this final rule, EPA has revised § 174.479 to clearly state that the recipient plant must be a food plant by including the phrase ''recipient food plant'' in the regulatory text at § 174.479(a) and (b). In the final rule, EPA has revised the definition of ''food plant'' proposed in the 1994 proposed rule at 40 CFR 180.1137 (59 FR at 60542) to read: ''Food plant means a plant which, either in part or in toto, is used as food''. EPA includes this definition at 40 CFR 174.3. EPA also includes at § 174.3 the definition of food found in the FFDCA. Thus, for these regulations for plant-incorporated protectants: Food includes articles used for food or drink by humans or other animals.

6. *What is the status of substances within sexually compatible plant populations that might be used as inert ingredients?* In a companion document published elsewhere in this issue of the **Federal Register**, EPA describes its consideration of inert ingredients in light of existing regulations and comments received in response to both the November 23, 1994 **Federal Register** document (59 FR 60534) and a 1996 supplemental document (61 FR 37891) discussing the Agency's treatment of selectable markers as inert ingredients for plant-incorporated protectants. In the companion document published elsewhere in this **Federal Register** on FIFRA regulations, EPA describes its determination that it will apply the concept of inert ingredients to plant-incorporated protectants consistent with the 1994 proposal.

The preamble discussion in the 1994 **Federal Register** document (59 FR at 60523) of the rationale supporting the proposal to exempt plant-incorporated protectants derived from sexually compatible plants extends to any substance that is derived from plants sexually compatible with the recipient plant, including substances such as a selectable marker, used to confirm or ensure the presence of the active ingredient. EPA's analysis in Unit IX., applies equally to all the substances that normally are found in a population of sexually compatible plants, including inert ingredients as long as these are derived through conventional breeding from plants sexually compatible with the recipient plant, and have never been derived from a source that is not sexually compatible with the recipient plant. An example of such an inert ingredient in sexually compatible populations could be tightly linked traits, such as unusual leaf pigmentation always found with a pest resistance trait.

EPA includes these residues at 40 CFR part 174, subpart X, to ensure that readers understand that any trait used as a selectable marker, and the genetic material necessary to produce it, that occurs normally in a plant sexually compatible with the recipient plant or is introduced through conventional breeding, is exempt from the FFDCA section 408 requirement of a tolerance, as well as FIFRA requirements on inert ingredients when used with a plant-incorporated protectant derived through conventional breeding from a plant sexually compatible with the recipient plant. EPA believes this interpretation is a logical implication of the preamble discussion in the 1994 proposed rule (59 FR at 60538).

Because the Agency recognizes that a substance described in Unit IX.B.2. (i.e., a toxicant) could theoretically be used as an inert ingredient, EPA places the same limiting condition on residues of the inert ingredient in food as is placed on residues of the pesticidal substance portion of the active ingredient; i.e., the residues of the inert ingredient do not qualify for the exemption if they are present in food from the plant at levels that are injurious or deleterious to human health.

Discussion supporting this exemption can also be found in a companion document published elsewhere in this issue of the **Federal Register** on FIFRA regulations for plant-incorporated protectants. Regulatory text has been established at 40 CFR 174.485, subpart X, which is entitled ''Inert ingredients from sexually compatible plant,''in a companion document on FIFRA regulations for plant-incorporated protectants published elsewhere in this issue of the **Federal Register**.

D. What Were the Other Potential Approaches to the Scope of Exemption?

In the November 23, 1994 **Federal Register** document (59 FR 60537), EPA discussed the merits of an approach using taxonomy, along with sexual compatibility (Option 2), as a standard for describing closely related plants, and received comment on use of such a criterion. EPA also received a comment, made in the context of the FIFRA regulations, suggesting that the criterion of sequence homology be used to limit the concept of sexual compatibility. In light of the relevance of this comment to this FFDCA exemption, EPA discusses this suggestion, as well as the comments on taxonomy, here. EPA also discusses a comment suggesting that EPA consider extending the exemption, on a case-by-case basis, to residues of plant-incorporated protectants derived from plants unrelated to the recipient plant, and a suggestion that exemptions should be based on a documented history of safe use.

1. *Taxonomy*. Two commenters expressed reservation about using a taxonomic standard for describing closely related plants. They pointed out that taxonomic categories, and the relationship of a given plant species to a given taxon, may be transient since taxonomic classification may change as information accrues. EPA agrees. In the 1994 **Federal Register** document, EPA noted (59 FR at 60524) that a taxonomy-based standard (e.g., Option 2) may be artificial: classification of plants in different taxonomic genera is not fixed and could change over time and between scientific authorities. Taxonomy reflects current observations about phenotypic, and to some extent, genotypic, differences between organisms. Currently, some plant genera are narrowly defined; for other plant genera, membership is based on broader criteria. These differences in classification criteria may lead to different probabilities between genera that new exposures may occur when genetic material from one species in a genus is introduced into another species in the genus. In recent years new tools have become available to taxonomists, allowing them to better clarify phylogenetic relationships among organisms. New information, particularly that obtained through the use of new genetic tools, concerning organisms' properties and relationships may in the future alter current taxonomic designations. In light of these advances, EPA anticipates there may be some reorganizations among the Plantae, and that these reclassifications will better reflect the relationships

among plants, and the probability of new exposures in intrageneric crosses.

The possibility that taxonomic classification may change as information accrues would add an extra layer of complexity to any regulations based on a taxonomic standard, and EPA probably would not be able to structure an exemption to accommodate for potential changes in classification. The possibility of reclassification also creates some uncertainty within the regulated community about the future status of a product.

Furthermore, under the FFDCA, an exemption must be examined specifically within the context of the food supply and dietary consumption. Although some species in a genus might be food plants, others in that genus might not. Moreover, in a genus containing food plants, there may be such barriers to hybridization that some of the non-food species in that genus would never have contributed to the food supply. Thus, there may be no experience with the potential dietary risks associated with such non-food species. In addition, knowledge of whether substances such as naturally-occurring toxicants are present is, in general, more limited for all the plant species constituting a genus than it is for species used to produce the major food crops. Consequently, there is a greater degree of uncertainty in any finding applicable to all potential members of taxonomic categories. The large body of information supporting this exemption was generated for food crops in sexually compatible populations (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19, for example). Overall, the base of dietary experience is not as broad or as deep for populations of plants described by the taxonomic standard of genus as it is for populations of plants described by sexual compatibility. EPA does not believe it possesses sufficient information at this time to allow the Agency to issue an exemption based on taxonomy.

2. *Sequence homology*. EPA received one comment suggesting that an additional criterion be used to limit the concept of sexual compatibility. While this suggestion was made in the context of a comment made on the proposal to exempt plant-incorporated protectants derived from plants sexually compatible with the recipient plant from FIFRA requirements, EPA discusses that suggestion here because of its relevance to EPA's decision to exempt residues of pesticidal substances derived through conventional breeding from plants sexually compatible with the recipient plant. The suggested criterion of sequence homology would base relatedness on the degree of sequence homology between the source and recipient plant. Sequence homology refers to the extent that the sequence of deoxynucleotides in two pieces of genetic material are the same. A deoxynucleotide is made up of a sugar, a phosphate, and one of four purine or pyrimidine bases (adenine, cytosine, guanine, thymine). The sugars and phosphates of the deoxynucleotides are covalently linked by phosphodiester bonds to form the ''backbone'' of the deoxynucleotide polymer (DNA). One base is attached to each sugar in the sugar-phosphate backbone. The information encoded in the genetic material is determined by the sequence in which the bases are attached to the sugar-phosphate backbone. The extent to which two pieces of genetic material have the same base sequence is often described in terms of percent homology, with 100% homology meaning the pieces of genetic material have an identical sequence. The Agency currently believes that DNA sequence homology is a less straightforward standard for regulatory purposes than a standard such as sexual compatibility. Sexual compatibility is known in most cases, and if it is not, it is less burdensome and simpler to demonstrate than is relatedness based on DNA sequence homology. Use of homology as a criterion presents the following complex issues. First, where should homology be assessed? For example, how many genes of the source and recipient plants should be compared to determine the degree of homology? All the genes of both plants? A few genes? If only a few, which genes? Second, what degree of homology would be sufficient to indicate a high degree of relatedness? Third, under what conditions should homology be measured? Fourth, appropriate test procedures would need to be developed and validated in order to set a standard procedure for measuring homology. All of these issues would need to be resolved, and converted into regulatory text, in order to develop an exemption standard based on DNA sequence homology.

3. *Other potential exemptions suggested by comment*. One comment suggested that EPA consider extending the exemption, on a case-by-case basis, to residues of the pesticidal substance portion of plant-incorporated protectants derived from plants unrelated to the recipient plant: ''Should a gene be taken from a commonly consumed food plant and inserted into another commonly used food plant, and the trait is expressed at approximately the same (or lower) level, an exemption would be warranted.'' A second commenter proposed that exemptions should be based on a documented history of safe use.

With regard to the suggestion that EPA consider extending exemptions on a case-by-case basis to residues of pesticidal substances of plant-incorporated protectants derived from plants unrelated to the recipient plant, the Agency has the option to exempt residues of pesticides from the requirement of a tolerance on a case-by-case basis provided that the residues meet the exemption standard in FFDCA section 408(c). In addition, any person may petition EPA to establish a tolerance exemption pursuant to section 408(d). Section 408(d)(2)(A) establishes the minimum requirements for such a petition. As additional information becomes available, EPA will consider, in future, exempting from the FFDCA requirement of a tolerance, residues of plant-incorporated protectants derived from plants unrelated to the recipient plant when these can be shown to meet the FFDCA section 408 safety standard. EPA also has the option of exempting residues of plant-incorporated protectants based on a history of safe use where there is sufficient information to meet the FFDCA section 408(c) test.

IX. Statutory Finding

A. What Methodology Did EPA Use to Assess these Residues?

For most pesticides (e.g., chemical pesticides), EPA's dietary risk evaluation relies on data generated by testing in laboratories using representative animal models to estimate acute, subchronic or chronic hazard end-points (e.g., acute toxicity, carcinogenicity, developmental toxicity). Conclusions from animal models are used to assess dose-response and describe such endpoints for potential human hazard. Other information, including residue data and information generated by use of mathematical models, are used to develop human exposure estimates. These exposure and hazard components are combined to quantify the potential risk associated with the pesticide's use. Uncertainty factors are often used in the risk assessment to account for extrapolation from animal models to human toxicity and from limited studies using humans to the larger population. The data requirements describing the types of information to be generated and other guidance for assessing dietary risk are detailed in 40 CFR part 158.

The questions posed as part of the risk assessment in evaluating residues of

most pesticides (e.g., chemical pesticides) can also be posed for the pesticide chemical residues that are the subject of this exemption, and 40 CFR part 158 can be used as guidance in evaluating these residues for hazard end-points (including, for example, acute toxicity, carcinogenicity, and developmental toxicity). To address the hazard endpoints described in 40 CFR part 158 for residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, EPA relied on a very large body of information found, for the most part, in the public scientific literature. In performing the assessment for this exemption from the requirement of a tolerance, EPA did not need to rely as much on information generated from animal models as it would in assessing other pesticides (e.g., chemical pesticides). A very large body of experience with actual human dietary consumption over hundreds, if not thousands, of years exists for the substances that are the subject of this exemption. And thus, a large and varied amount of information developed through systematic scientific study exists in the literature, and can be used for assessing the risk of exempting these residues. Numerous epidemiological studies on humans show the health benefits of consuming foods containing residues of the plant-incorporated protectants that are the subject of this exemption (Refs. 11, 12, 13, 14, 15, 16, 17, 18, and 19). The epidemiological studies in particular provide information on the effects of chronic exposure of a far longer term than is possible with animal model experimentation, given the large differences in life span between humans and most animals used in animal model testing. The results of many nutritional assessment studies using human volunteers are available on the effects of either whole foods from plants in sexually compatible populations or isolated constituents from food from such plants (Refs. 11, 12, 13, 14, 15, 16, 17, 18, and 19). Studies have also been performed using animal models to test the effects of either whole foods from crops in sexually compatible populations or constituents from food from such crops (Refs. 11, 12, 13, 14 15, 16, 17, 18, and 19). There is a large literature on constituents of food from plants in sexually compatible populations accumulated by a century of systematic study (Ref. 8), and EPA also used these sources of information.

EPA also considered other information in the literature in evaluating the potential for exposure to residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. Plant-incorporated protectants are produced within the living plant itself and the pesticidal substance is used *in situ* in a living plant to protect against pests, in contrast to most other pesticides which must be applied to the plant (Ref. 20). Because a plant-incorporated protectant is produced and used within the plant, physiological constraints limit the amounts of residues produced by the plant (Ref. 20). Because the plant-incorporated protectant is within the plant, routes by which other organisms may be exposed to the plant-incorporated protectant may be more limited, e.g., dietary exposure is likely to be the predominant route of exposure.

EPA used experimental data derived from the science of phytopathology to characterize the disease and pest resistance mechanisms known to occur in plants (Ref. 21). EPA also considered information from the field of plant physiology regarding plant metabolism, the production of substances that may have pesticidal effects, and conditions that may limit the plant's production of such substances (Refs. 7 and 20). This information also provided a basis for EPA's estimation of the physiological limitations to production in plants of substances that may be pesticidal and thus to production of their residues. EPA also used information from the fields of biochemistry, microbial ecology, and ecology (Refs. 7, 21, and 37).

EPA's conclusion that the vast majority of plant varieties developed by conventional breeding in sexually compatible populations produce foods that are safe for human consumption is based on this information and the historical consumption of crops since the prehistorical origins of agriculture. EPA also considered its knowledge of the practices that plant breeders routinely employ in selecting and developing plant varieties in sexually compatible plant populations, such as chemical analyses, taste-testing, and visual analyses, and that such practices have historically proven reliable for ensuring the safety of food from such plants (Refs. 8 and 22). EPA also considered that appropriate processing procedures are widely known and are routinely used by consumers in preparation of food containing residues that are the subject of this exemption, including those foods which require specific processing and/or preparation steps to avoid dietary problems.

Residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants were evaluated for dietary risk within the context of the food supply and dietary consumption patterns. In performing its assessment, the Agency considered that the diet includes all of the food items that are customarily eaten by human populations or subpopulations as part of a normal diet. (EPA did not consider that the normal diet includes plants or plant parts consumed in times of deprivation, for religious reasons, in substance abuse or by misidentification. The information base on which EPA relied in performing its risk assessment (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19, for example) did not address such plants.)

EPA considered health risks to the general population, including infants and children. Children, and to some extent infants, have always and currently consume food containing residues that are the subject of this exemption. EPA's risk assessment also included subgroups as part of the general population, (i.e., differences in diet due to the influence of culture), and allowed for consumption pattern differences of such subgroups. The consumption of food plants is part of a balanced and varied diet.

EPA believes that the numerous epidemiological and nutritional assessment studies found in the literature of human experience in consuming food containing residues that are the subject of this exemption, combined with information generated from animal model testing and biochemical studies and knowledge from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry, and plant breeding form the appropriate information base for evaluating the potential risks of such residues.

B. What Factors Has EPA Considered in Making the Findings Required by 408(c) of the FFDCA?

FFDCA section 408(c)(2)(B) requires EPA to consider several factors in determining whether to exempt a pesticide from the requirement of a tolerance (21 U.S.C. 346a(c)(2)(B)). Information relevant to EPA's consideration of these factors with regard to this exemption of the pesticide chemical residues of a plant-incorporated protectant derived through conventional breeding from sexually compatible plants, is contained in this document, as well as in other

documents in the record for this rule as described in Unit X.

The preamble discussion in the 1994 **Federal Register** document (59 FR at 60538), and in the May 16, 1997, supplemental document (62 FR 27132), of the rationale supporting the proposal to exempt residues of plant-incorporated protectants derived from sexually compatible plants extends to any substance that is normally a component of a population of sexually compatible plants. It thus, applies to any substance, such as a selectable marker, used to confirm or ensure the presence of the active ingredient, that is also derived from plants sexually compatible with the recipient plant. EPA's analysis in Unit IX., applies equally to all the substances that are normally a component of a population of sexually compatible plants, including inert ingredients as long as these are derived through conventional breeding from plants sexually compatible with the recipient plant, and have never been derived from a source that is not sexually compatible with the recipient plant.

1. *Validity, completeness and reliability of available data.* As described in Unit IX.A., EPA's risk assessment for residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants was based primarily on an analysis of the long human experience with breeding and growing agricultural plants and preparing and consuming food from such plants, and associated epidemiological studies, nutritional assessments with human volunteers and animal model testing (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19). EPA combined this information with knowledge from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry (including studies on the constituents of food), and plant breeding to evaluate the potential risks of pesticide chemical residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. EPA considered the validity, completeness and reliability of the available information on human consumption of food containing substances that are the subject of this exemption including epidemiological studies, nutritional assessments with human volunteers and animal model testing, as well as information from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry (including studies on the constituents of food) and plant breeding. EPA concluded that this information was valid, complete and reliable, and adequately addressed the issues of hazard and exposure with regard to residues in food of plant-incorporated protectants derived through conventional breeding from sexually compatible plants.

2. *Nature of toxic effect.* In light of comments raising concern about possible adverse effects from increases in the levels of substances that naturally occur at low levels in food from plants, EPA considered the nature of toxic effects shown by the data described in Unit IX.B.1., above to be caused by substances that might potentially be residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, should these substances be used as pesticides (i.e., if humans intend to use these substances for preventing, repelling or mitigating any pest) and present at high levels. The examination led EPA to conclude that as the vast majority of substances in plants are not toxic, any of these nontoxic substances, should they be used as plant-incorporated protectants, would not present toxic effects. EPA has identified 21 substances of plant origin that are in foods that could be considered part of a normal diet and could potentially present toxic effects if present at high levels (Ref. 8). (The normal diet does not include plants, or parts of plants, consumed in times of deprivation, for religious reasons, in substance abuse, or by misidentification. The normal diet is considered to be balanced and varied and include food from a variety of sources.) This analysis is based on an accumulation of millennia of human experience and a century of systematic scientific study of food constituents (Ref. 8). The conclusion of the analysis described in Unit IX.B.2., for these 21 substances indicates that they are either: Beyond the scope of the exemption; in foods that are not part of the normal diet of the United States population; and/or, millennia of human experience and use have given rise to procedures, on the part of the plant breeder, the food processor and/or the consumer, that combined with the condition determining eligibility for this exemption, adequately address the risk posed by these substances.

These 21 substances, of the hundreds of thousands of plant-produced substances in food, represent less than one-tenth of 1% of the total number of constituents of food (Ref. 8). Of these 21 substances, seven (acetylandromedol, andromedol, anhydroandromedol, desacetylpireistoxin B, gelsamine, tutin, hyenanchin) are in honey, being ''pass-through'' contaminants of honey introduced by bees collecting pollen from rhododendron, azalea, yellow jasmine, or the tutu tree. (The substances from the tutu tree, tutin and hyenanchin, can cause delirium and convulsions). Similarly, four (cicutoxin, coiinine, methylconiine, conhydrine) of the 21 substances capable of causing toxic effects in the normal diet are pass-through contaminants in the milk of cows that have consumed water hemlock or hemlock. These substances are nervous system stimulants. None of the plant sources of these 11 pass-through contaminants are used or intended to be used as food plants and thus this section 408 exemption does not apply to them. Another of the 21 substances in the normal diet identified as potentially causing toxic effects is nitrate. Exposure to excessive amounts of nitrates can cause methemoglobinemia, a condition in which some portion of the hemoglobin molecules become incapable of binding oxygen. Levels of nitrates high enough to cause such effects can be found in spinach and other green, leafy vegetables subjected to intensive application of high-nitrate fertilizers. Nitrates that enter the plant through uptake of fertilizer applied intensively are not ''produced'' by the plant per se, i.e., they are not biosynthesized by the plant. This exemption is not relevant to such nitrates. The toxic effect presented by high levels of nitrates is generally addressed in agriculture by use of proper fertilization practices.

Of the 21 substances originally identified (Ref. 8), nine of these (solanine, linamarin, lotaustralin, cucurbitacin, vicine, convicine, hypoglycin A, sparteine, beta-N-oxalylamino-L-alanine) are biosynthesized by plants that could be used as food in a normal diet somewhere in the world, and, thus, if used by humans for pesticidal purposes, could potentially be pesticide chemical residues derived through conventional breeding from sexually compatible plants. Three of these nine substances (sparteine, hypoglycin A, beta-N-oxalylamino-L-alanine) are found in food not customarily consumed as part of the normal diet in the United States. Their risks appear to be well known locally where plants containing such substances are consumed, and native methods of processing exist to reduce the potential for toxic effects (Ref. 22).

Sparteine is a quinolizidine alkaloid found in the lupines. The lupines are forage or range crops, but can also be cultivated for feed and have some limited use in human food, primarily as

a ''traditional'' grain used by indigenous cultures in South America and the Mediterranean. The presence in the plant of the quinolizidine alkaloids appears to protect the plant against fungal infection. Reduction of the levels of quinolizidine alkaloids in the plant can result in increased levels of potentially more hazardous mycotoxins. Toxic effects from consumption of food containing higher levels of sparteine include breathing problems, weakness and loss of motor control (Ref. 22, 23). These alkaloids can be removed by cooking, or by rinsing for several days (Ref. 22, 24).

Beta-N-oxalylamino-L-alanine is found in the seeds of the chickling vetch. It is a neurotoxin that can cause spastic paralysis, probably by interfering with the action of the neurotransmitter, glutamate (Ref. 22, 25). Reported cases of toxicity are mostly confined to the Indian subcontinent. Most of the toxin can be leached out by soaking the seeds in hot water for several minutes, followed by cooking.

Hypoglycin A is an amino acid analogue found in the immature ackee fruit that can result in severe hypoglycemia and vomiting. Ackee fruit is primarily consumed in Africa and Jamaica (Ref. 22). The primary method of dealing with the potential adverse effect presented by hypoglycin A is avoidance of (i.e., not consuming) immature ackee fruit.

Of the remaining six substances, two (vicine and convicine) affect a small subpopulation of the United States population. Vicine and convicine are found in the fava bean. Exposure of individuals with the Mediterranean form of an inherited deficiency of the enzyme, glucose-6-phosphate dehydrogenase (G6PD), to these substances in the fava bean can result in an hemolytic anemia. The anemia is manageable (Ref. 26). Physicians attempt to prevent hemolytic episodes by warning patients with the Mediterranean form of G6PD deficiency about the risks of consuming fava beans (Ref. 27). Thus, the primary strategy employed by persons with this G6PD deficiency with regard to food is avoidance of (i.e., not consuming) foods containing fava beans. Drying the beans or exposing them to sunlight reduces the potential for hemolytic episodes (Ref. 22).

Several strategies, including breeding for varieties that produce low levels of the substances and monitoring, as well as general knowledge in the population, reduce the potential for toxic effects to occur with the remaining four toxicants (cucurbitacin, linamarin, lotastralin, solanine). Cucurbitacins are naturally present in edible squash and cucumbers at very low levels. Cucurbitacins are purgatives and impart a bitter taste to the fruit. Cucurbitacins if consumed at extremely high concentrations may cause stomach aches or cramps (Refs. 22 and 28). On rare occasions, in producing seed for cultivated varieties, pollen from a wild relative may contaminate the seed plot, resulting in seeds that may produce higher levels of cucurbitacin. Breeding isolation is employed by seed producers to ensure that such contamination does not occur (Refs. 7 and 22).

Linamarin and lotaustralin (also called phaseolutin) are cyanogenic glycosides (Refs. 8 and 22) biosynthesized by cassava and lima beans. When the plant tissue is damaged, enzymes are released that act on the cyanogenic glycoside to produce hydrogen cyanide. The toxicity of cyanide is due to its ready reaction with the iron atom of the enzyme, cytochrome oxidase. The ability of the cell to utilize oxygen is inhibited by formation of the cytochrome oxidase-cyanide complex. Toxic effects associated with cyanide include neurological disorders, breathing difficulties, and thyroid enlargement (Ref. 22). The lima bean varieties on the United States market today were bred and are monitored to ensure that they produce very low levels of cyanogenic glycosides (Refs. 22 and 29). Imported lima beans are monitored to ensure only low levels of cyanogenic glycosides (Refs. 22 and 29). Similarly, cassava used in the United States today comes from varieties that were bred and are monitored to ensure that they produce very low levels of cyanogenic glycosides. Populations outside of the United States (e.g., Africa) that consume cassava from varieties that produce higher levels of cyanogenic glycoalkaloids are aware of the risk associated with this food and use native methods of processing (peeling, chopping and grinding in running water, also boiling and fermentation) to reduce the cyanogenic glycoside content. Cases of toxicity are observed primarily in these populations when the cassava is eaten without adequate processing, because a scarcity of other food items causes individuals to risk consuming inadequately processed cassava to ease their hunger (Ref. 26). There are also ongoing breeding and monitoring efforts to assist these populations to reduce the cyanogenic glycoside content in cassava varieties grown in their countries.

The glycoalkaloids collectively referred to in this document as solanine are biosynthesized by potatoes, and to some extent eggplant and peppers. A related glycoalkaloid, tomatine, can be found in green tomatoes. The solanines are membrane disruptors. Some members of the class have been shown *in vitro* and through intraperitoneal and intravenous injection to be weak to moderate cholinesterase inhibitors (Ref. 30). While solanine poisoning is very rare, in large doses solanine can cause gastrointestinal tract irritation, including moderate nausea, vomiting and diarrhea, as well as headaches, drowsiness, sweating, changes in blood pressure and heart rate, and edema (Ref. 22). Solanine imparts a bitter taste to the tuber, and at high concentrations solanine can leave a persistent irritation and burning sensation on the tongue (Ref. 22). Potato varieties are bred and monitored in the United States to ensure that they produce only low levels of solanine (Refs. 22 and 31). Monitoring for these glycoalkaloids also occurs during the grading and shipping of potatoes. Peeling or removing any damaged portion of the potato is the best way to reduce solanine levels. In an undamaged, unsprouted potato, thirty to eighty percent of the solanine is found in, and directly under, the skin. Cooking, e.g., boiling in steam or water or deep frying in oil at 170 degrees, may lower solanine concentrations (Refs. 22 and 32).

For the reasons described in the preceding paragraphs, EPA does not believe that this exemption would result in levels in food of residues of these four substances significantly different from those observed in food currently safely consumed. That there have been few instances in the United States of toxic effects on humans due to substances normally found in food from plants in sexually compatible populations in the past 50 years, despite the hundreds of food plant varieties from sexually compatible plant populations going onto the market each year (Ref. 8), supports a conclusion that the probability of risk is low even for the few substances discussed in this Unit. As an added protection, EPA has placed a condition limiting the exemption to residues present in food from the plants at levels that are not injurious or deleterious to human health.

3. *Relationship of studies to humans.* EPA considered the available information concerning the relationship to human risk of this information on residues in food of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. The effect of these residues on humans was assessed in light of the long history of human

consumption of food derived from plants, and from products such as meat and milk from animals that consume forage and other crops (e.g., corn and other grains), containing residues that are the subject of this exemption, and associated epidemiological studies, nutritional assessments with human volunteers and animal model testing (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19). The epidemiological studies and nutritional assessments performed with human volunteers supply data generated on humans and, thus, directly applicable to humans. Information from animal model testing as well as information from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry (including studies on the constituents of food) and plant breeding were also used to predict effects on humans. Because information on human consumption of food derived from plants comprising sexually compatible populations was available and adequately addressed the issues of hazard and exposure for residues that are the subject of this exemption, the Agency relied primarily on the epidemiological and other information generated directly from humans rather than relying on data generated in the laboratory through animal testing.

4. *Dietary consumption patterns*. EPA considered the available information on the varying dietary consumption patterns of consumers and major identifiable consumer subgroups as it pertains to residues that are the subject of this exemption. The consumption of food from plants is part of a balanced and varied diet (Ref. 33). Humans have been consuming food containing substances that may be residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants and thus, all consumers, and all major identifiable consumer subgroups, are, and have been, exposed to the substances that are the subject of this exemption. It is not anticipated that publication of this exemption from the requirement of a tolerance will affect current consumption patterns of food from crop plants by consumers or major identifiable consumer subgroups, and thus no differences in exposure patterns are anticipated.

5. *Available information concerning cumulative effects of the pesticide chemical residue and other substances that have a common mechanism of toxicity.* EPA examined available information on the cumulative effect of residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, as well as other substances present in food that may have a common mechanism of toxicity with such residues.

i. *What information is available on the cumulative effects of the residues that are the subject of this exemption?* A large amount of information exists for the residues that are the subject of this exemption. The extensive information described in Unit IX.A. and Unit IX.B.1., e.g., epidemiological studies, nutritional assessment studies and animal model testing (Refs. 11, 12, 13, 14, 15, 16, 17, 18, and 19) indicates a very low probability of harm. The few substances occurring naturally in food from plants that EPA has identified as being problematic are discussed in Unit IX.B.2. A discussion of the variation in the levels of substances that may be pesticide chemical residues and may occur naturally among the plants of a sexually compatible population, and the potential consequences of that variation are discussed in Unit IX.B.6.

If information becomes available that indicates its analysis of cumulative effects in Unit IX.B.5., is no longer consistent with the FFDCA exemption standard for residues of a pesticidal substance in this category, EPA will consider the validity of the new information and may act to amend this tolerance exemption.

ii. *Are there substances that occur naturally in food that may share a common mechanism of toxicity with residues that are the subject of this exemption?* Because of the conditions of this exemption, i.e., the genetic material leading to the production of the plant-incorporated protectant is derived through conventional breeding from plants sexually compatible with the recipient plant, the potential for new dietary exposures is low. Thus, EPA considered the effects of all the substances in food from plants when it addressed the safety of food from plants in sexually compatible populations, including those that occur naturally in plants along with the substances that are the subject of this exemption. Food from plants has hundreds of thousands of constituents, and EPA cannot rule out the possibility that in the foods humans consume, common mechanisms of action might exist between some of these substances and the various residues that are the subject of this exemption. For example, the word ''solanine'' generically refers to a group of related steroid glycoalkaloids that naturally occur in plants in the nightshade family such as potatoes, eggplant, peppers and green tomatoes. EPA's analysis considered the effects of these substances in food from plants cumulatively when it addressed the safety of food from plants in sexually compatible populations.

Food from plants in sexually compatible populations is being safely consumed by humans either directly, or indirectly in products such as meat and milk that are derived from animals that consume forage and other crops (e.g., corn and other grains). The history of safe consumption and the information base described in Unit IX.A. and Unit IX.B.1. indicates that any cumulative effects between substances in food that may have a common mechanism with residues that are the subject of this exemption present a very low probability of harm. The analysis made in this preamble in Unit IX.B.6., concerning potential increases in levels of residues apply equally to constituents of food that may have a common mechanism of action with residues that are the subject of this exemption. Variations in the levels of these substances are not expected to be any different than those currently observed in conventional breeding. Experience has shown that food from crop plants in sexually compatible populations is safe for human consumption and/or appropriate processing procedures are widely known and routinely used by processors and consumers in preparing food from such sources. Should EPA in the future identify substances with a common mechanism of toxicity with the residues that are the subject of this exemption, both FIFRA and the FFDCA give the Agency adequate authority to take appropriate action to address any risks these substances may present to human health. Should substances in food that may share a common mechanism of toxicity with residues that are the subject of this exemption present cumulative effects resulting in food safety concerns, the condition limiting this exemption at 40 CFR 174.479 and the requirement to report adverse effects at § 174.71 will provide a mechanism to monitor the effects of this class of products and allow the EPA and FDA to act expeditiously.

iii. *Are there substances that do not occur naturally in food that may share a common mechanism of toxicity with residues that are the subject of this exemption?* EPA examined two groups of substances to determine whether these substances have a common mechanism of toxicity with residues that could be the subject of this exemption.

a. *Do the organophophate and carbamate pesticides have a common mechanism of toxicity with the naturally occurring toxicants solanine?* EPA examined certain of the

organophosphate and carbamate pesticides and the naturally-occurring toxicants, solanine (described in Unit IX.B.2.). EPA examined these substances because many members of these two classes of pesticides inhibit the cholinesterase enzymes (Refs. 30 and 34), and some *in vitro* and intraperitoneal and intravenous injection studies have shown that some of the glycoalkaloids comprising the solanines also can inhibit these enzymes (Refs. 22 and 30). The solanines have also been shown to disrupt cell membranes (Ref. 30).

EPA examined available information generated both *in vitro* and through *in vivo* animal studies on solanine. EPA gave greater weight in its analysis to information generated by animal studies where the animals were exposed through oral ingestion, as such studies are far more likely to provide physiologically significant information. Animal studies performed with the solanines administered to the animals in similar manner that plant-incorporated protectants would be presented in the diet (i.e., through ingestion) show that death could not be attributed to cholinesterase inhibition and its neurotoxic consequences but was due to severe gastrointestinal necrosis from cell membrane disruption (Ref. 35).

Given this information, EPA has concluded that available information is insufficient to create a presumption of the existence of a common mechanism of toxicity between solanine and the organophosphate and carbamate pesticides (Ref. 36), particularly as animal studies suggest the solanines, when used as plant-incorporated protectants, lead to the endpoint of death through membrane disruption.

b. *Do microorganisms have metabolic pathways in common with plants?* One commenter, in response to the May 16, 1997, supplemental document, suggested that some microorganisms may have some metabolic pathways in common with plants, although the commenter was of the opinion that this is not likely to be problematic. EPA agrees that this route of exposure to any substances that may be related to residues that are the subject of this exemption is unlikely to be problematic, and notes that possession of the same metabolic pathways does not equate to expression of the same characteristics. Raw plant foods commonly contain hundreds to several million microorganisms per gram (Ref. 8). Some of these microorganisms are commensals of the plant, others come from the natural environment of the plant (e.g., soil, water, air, other plants). Such microorganisms are routinely consumed with raw agricultural produce. Certain microorganisms are deliberately consumed routinely in high numbers by humans with no ill effects (e.g., Marmite based on a yeast, natto based on the bacterium *Bacillus* subtilis, yogurt made with bacteria of the genus *Lactobacillus*, cheese made with the fungus *Penicillium roquefortii*). This base of experience with actual human consumption indicates that should such microbes have any metabolic pathways in common with foodstuffs from plants, the cumulative effect of substances from these pathways with residues that are the subject of this exemption, presents a very low probability of harm.

c. *Are there any other substances?* EPA cannot rule out the possibility that there may be other substances outside of the food supply that may have a common mechanism of toxicity with the residues that are the subject of this exemption, although it is not aware of any other such substances. Should EPA in future identify substances with a common mechanism of toxicity other than those found in food plants, both FIFRA and the FFDCA give the Agency adequate authority to take appropriate action.

6. *Aggregate exposures of consumers including non-occupational exposures.* EPA considered the available information on the aggregate exposure level of consumers to the residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, including exposure to these substances in plants when they are not intended to be used as plant-incorporated protectants (i.e., when humans are not intending to use the substance for a pesticidal purpose). This evaluation included a consideration of exposures from dietary sources as well as from other non-occupational sources. Plant-incorporated protectants and their residues are likely to present a limited exposure to humans. In most cases, the predominant, if not the only, exposure route will be dietary. Exposure through other routes is likely to be negligible because the substances are in the plant tissue and thus are found either within the plant or in close proximity to the plant.

In addition, the substances evolved by populations of sexually compatible plants are part of the metabolic cycles of these plants. These substances are biotic and are subject to the processes of biodegradation and decay that all biotic materials undergo (Ref. 37). Biotic materials are broken down to constituent parts through the enzymatic processes of living organisms, and these constituent parts used as the building blocks to make other biotic substances.

Because of their biodegradable nature, the residues that are the subject of this exemption do not bioaccumulate (bioaccumulation occurs when a substance is taken into the body through processes such as eating, and as the body is unable to either break the substance down or eliminate it, the substance accumulates in the tissues) or biomagnify in the tissues of living organisms (biomagnification occurs when a substance bioaccumulates in the bodies of organisms lower in the food chain, and as predators higher in the food chain consume organisms lower in the food chain, more and more of the substance accumulates in the bodies of organisms higher in the food chain) as do such long-lived persistent substances such as DDT (Ref. 38). Humans ingesting the substances that are the subject of this exemption are likely to quickly degrade them and use their constituent elements as nutrients. Because of these characteristics, the potential for exposures to the residues to occur, beyond direct physical exposure to, or consumption of, the plant, is limited. This also contributes to EPA's conclusion that non-dietary exposure (i.e., non-food oral, dermal and inhalation) in non-occupational settings is likely to be negligible.

i. *Dietary exposures?* As described in Unit IX.A. and Unit IX.B.1., a large base of experience exists, including information on human dietary exposure, for the residues exempted by this action. Moreover, dietary exposures other than those for which a large base of information exists, are unlikely to result from this exemption for residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. Plants in a sexually compatible population are likely to have similar genetic information and have many traits in common. Generations of directed breeding to produce improved crops for cultivation have tended to increase the relatedness, and reduce the genetic variability, of populations of agricultural crop plants (Ref. 6). Sexually compatible plants share a common pool of genetic material, and movement of genetic material encoding pesticidal substances between plants in a sexually compatible population through conventional breeding is unlikely to result in exposure of humans consuming food from such plants to residues to which no humans previously has been exposed and to which the information base underlying this exemption cannot be applied. The SAP Subpanel and the BSAC

Subcommittee at the joint meeting held on January 21, 1994, supported this conclusion and noted that genetic mapping of the genomes of both wild and crop plants reinforce the thesis that plants in sexually compatible populations are likely to possess similar genetic information (Ref. 6). It is likely that substances that are the subject of this exemption are present at low concentrations in the edible parts of plants, and that such substances have long been part of the human diet. There is no evidence at present in the many studies performed on the relationship of diet to health that food from plants in sexually compatible populations, properly handled, has any significant adverse health effect (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19).

The primary exposure consideration associated with the substances that are the subject of this exemption is whether the substances, identified in Unit IX.B.2. as toxic at higher concentrations, are likely to be present in food from plants in sexually compatible populations at such concentrations. EPA carefully examined whether there are variations, within and among food plant varieties in sexually compatible plant populations, in levels of plant-incorporated protectants and thus in the residues that are the subject of this exemption from the FFDCA requirement of a tolerance (Ref. 20). The amount of any substance produced by plants normally varies among members of a sexually compatible plant population because of the effects of conditions such as genetic constitution and environment (e.g., weather) (Refs. 8 and 20). Indeed, such variation is observed among plants of the same variety. For example, one researcher (Ref. 8) has shown a 20-fold variation in the amount of ascorbic acid (3 to 61 mg/100g tissue) in different varieties of muskmelon. Because such variation is ubiquitous in populations, differences in the levels of exposure to substances in plants are likely when humans consume food from plants, including differences in exposure to residues that are the subject of this exemption. Such variation is a natural phenomenon common to all plants, however, in controlled food production the variation in the substances identified in Unit IX.B.2. is limited (Ref. 22).

EPA also examined whether the levels of substances any variety within a sexually compatible population could produce are likely to exceed the range of low concentrations found in crop plant varieties safely consumed. For the following reasons, the Agency concluded that such occurrences were unlikely. First, there are several constraints on the extent to which expression of any substance can be increased in highly managed food crop plants without unwanted effects on other, desirable characteristics of the plant such as yield or palatability. In general, breeders balance a number of characteristics (e.g., yield, palatability, height, uniformity of seed drop) in developing marketable plant varieties. Solanine and cucurbitacin, for example, affect palatability as they taste bitter to humans.

Moreover, in conventional breeding, plant breeders assess the new cultivar for food safety, based in part on knowledge of and familiarity with the characteristics of agricultural plants in sexually compatible populations (Ref. 22). EPA's assessment of the likelihood of breeders ensuring that plants developed through conventional breeding will continue to be safe for consumption is supported by the record of safety of the food products from plants in sexually compatible populations. Although hundreds of new varieties come on the market each year, within the past 50 years, conventional plant breeding of plants in sexually compatible populations has recorded very few instances of plant varieties causing food safety problems. The two identified instances (Ref. 8), high psoralen expressing celery that in the 1980s caused dermatitis in grocery employees and the Lenape potato in the late 1960s with increased glycoalkaloid levels, involved increases in the level of known toxicants (which may or may not be plant-incorporated protectants depending on whether humans intend to use these substances for preventing, destroying, repelling or mitigating any pest). In both cases, the problem was identified and the appropriate measures taken to protect the public health. In the case of the Lenape potato, food processors in routine screening detected the high levels of solanine and the potatoes were removed from the market before exposure of consumers (Ref. 8). In contrast to these few problematic occurrences, there are many studies indicating the health benefits of consuming plant foods that likely contain residues that are the subject of this exemption (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19).

A second exposure consideration is whether this exemption will affect the ability of individuals with food sensitivities to manage these sensitivities. To protect themselves, individuals with food sensitivities generally avoid the food, and related foods, that cause them problems (Ref. 39). This exemption will not affect the efficacy of this strategy of avoidance, because the exemption will not affect the ability of individuals to recognize and avoid foods that cause them problems (Refs. 27, 39, and 40). For example, the ability of persons who have the Mediterranean form of the inherited G6PD deficiency to deal with their disease by avoiding (i.e., not consuming) fava beans or foods made with fava beans will not be affected. The substances in fava beans that can cause hemolytic anemias in such persons will be exempt only if they are moved through conventional breeding among fava bean plants and plant varieties sexually compatible with fava beans; a population of plants in which such substances normally occur, and the food of which individuals with the inherited G6PD deficiency avoid (Ref. 27). Similarly, the efficacy of the strategy of avoidance will not be affected for individuals suffering from food allergy (Ref. 39) or enteropathies such as celiac disease (gluten-sensitive enteropathy) (Ref. 40). Moreover, the efficacy of the monitoring, processing, and preparation methodology which humans are familiar with and have been adequate in the past to produce food safe for consumption will not be affected by publication of the exemption, e.g., the monitoring procedures for solanine used in the breeding and marketing of potatoes.

EPA believes the history of familiarity with agricultural plants in sexually compatible populations, and thus with the likely progeny of genetic exchanges between plants in such populations (Ref. 8), and the procedures currently employed in plant breeding to screen out undesirable traits in such populations, support a tolerance exemption for residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. However, to ensure that the Agency can act expeditiously should any rare instances of risk arise, EPA is placing at 40 CFR 174.479 a condition on this exemption from the requirement of a tolerance limiting the concentrations in food of substances such as toxicants that may be injurious or deleterious to human health. EPA is also implementing an adverse effects reporting requirement at § 174.71 that will serve to alert the Agency to any such rare instances of risk.

One comment received in response to the May 16, 1997, supplemental document (62 FR 27132), suggested that plant extracts might be used in some pharmaceutical preparations. The commenter did not provide any examples of these types of situations, nor any information on such extracts. Without such additional information, it

is difficult to determine whether the extracts would contain substances related to residues that are the subject of this exemption. However, even if such related substances are present in some pharmaceutical preparations, on a per person basis, the potential amounts involved in these exposures are likely to be a negligible contribution to aggregate exposure. The commenter also was of the opinion that such uses are not likely to be problematic.

ii. *Dermal exposure*. With regard to the dermal route of exposure, residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants may in some cases be present in sap or other exudates from the plant or the food 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 substances on a non-occupational basis. Although contact dermatitis can occur from such exposure (Refs. 41 and 42), these reactions are generally mild, of a self-limiting nature or self-diagnosed and treated.

Most of the substances that could be the subject of this exemption are unlikely to pass through the skin to affect other organ systems (Refs. 41, 42, and 43). For those substances which possess to some degree properties that allow some penetration of the skin, the potential amounts of such exposures, on a per person basis, are likely to be a negligible contribution to aggregate exposure, or do not present adverse effects.

There are a few substances with the ability to present an effect on dermal exposure on a non-occupation basis, that might be residues of plant-incorporated protectants, if humans intend to use these substances as pesticides. For example, one substance present in a food (condiment) Americans might use in preparing meals and identified as a potential skin irritant (Refs. 8 and 22) is the phenolic, capsaicin, found in cayenne pepper. Capsaicin is used medically in a topically applied cream, which facilitates passage of the capsaicin across the barrier of the outer layer of the skin, at concentrations of 0.025 to 0.075% capsaicin. The cream is applied up to four times daily for pain control and treatment of psoriasis (Refs. 22 and 44). Cayenne pepper can be used liberally in the diet. Currently, cayenne pepper is exempt from the requirement of tolerance when it is used on food crops (40 CFR 180.1165). Acute toxicity through the oral route has been examined in several animal species, and it is estimated that the lethal dietary dose for a 150 pound individual is 2.2 kilograms (Refs. 22 and 45). Given the low toxicity of capsaicin, even if capsaicin should penetrate through the barrier of the skin, aggregate exposure through the dermal and dietary routes is not anticipated to present harm.

A second substance examined because of known effects beyond mild dermatitis with dermal exposure are the psoralens. These substances occur naturally in a wide range of plants but occur in the highest concentrations in celery, dill and parsley (Refs. 22 and 41). Psoralens can be phototoxic to the skin in conjunction with sunlight (UV light). Due to their relative solubility in oils, psoralens can penetrate into the skin cells, where they intercalate into the genetic material of the skin cell (Refs. 22 and 41). Subsequent exposure to sunlight (UV light) causes the genetic material to ''cross link,'' affecting the ability of the cell to further process its genetic material. This may result in skin blisters and rashes. This UV-dependent phototoxicity has also been implicated in mutations that may lead to skin cancer (Refs. 22 and 41). In spite of the potential for this type of adverse effect with the psoralens, there are few reported incidents for substances derived through conventional breeding from sexually compatible plants (Ref. 8).

Psoralens (supervised and in small doses) are also used in the treatment of a variety of skin diseases, including vitiligo and psoriasis (Ref. 22), primarily through topical application.

The primary route through which humans in general are exposed to psoralens is dietary, and the psoralens are not toxic when ingested. Given the low oral toxicity, the supervised use of psoralen in medicine, the low concentrations of psoralen in celery, dill and parsley currently on the market, and the condition EPA has placed on this exemption limiting the amount of substances in food that may have an injurious or deleterious effect on human health, EPA finds that for psoralen, were this substance to be used as a plant-incorporated protectants derived through conventional breeding from sexually compatible plants, there is a reasonable certainty that no harm will result from aggregate exposure.

Those few substances from food plants discussed in Unit IX.B.2., which might be present in foods Americans might use in preparing meals and which at higher concentrations can cause adverse effects, do so when ingested (Refs. 22, 26, 29, and 31). Substances that are the subject of this exemption are unlikely to pass through the skin to affect target organs. For those substances which possess to some degree properties that allow some penetration of the skin, the potential amounts of such exposures, on a per person basis, are likely to be negligible in comparison to potential exposure through the dietary route, or do not cause adverse effects. Dermal exposures are, thus, unlikely to contribute significantly to aggregate exposure.

One comment received in response to the May 16, 1997, supplemental document (62 FR 27132) suggested that plant extracts might be used in some cosmetic preparations. The commenter was of the opinion that such uses are not likely to be problematic. The commenter did not provide any examples of these types of extracts, nor any information on the source or composition of such extracts. Without such additional information, it is difficult to determine whether the extracts would contain substances related to residues that are the subject of this exemption. EPA is aware that some floral extracts are used in perfumes, e.g., lavender, jasmine, rose. However, lavender, jasmine and rose are not generally consumed as staple foods, although parts of these plants can be brewed into teas or tisane. The amounts ingested through the tisane or by passing through the skin from perfumes is likely to be very small. Further, EPA is not aware of any reports of adverse effects from use of these flowers in tisane or perfumes. Even if such substances are present in some cosmetic preparations, on a per person basis, the potential amounts involved in these exposures are likely to be negligible.

EPA is also aware of other extracts used in perfumes from plants consumed as food, e.g., carrot, fennel, garlic, lemon. Even if such substances are present in some cosmetic preparations, on a per person basis, the potential amounts involved in these exposures are likely to be a negligible contribution to potential exposure through the dietary route.

iii. *Inhalation exposure*. With regard to exposure through inhalation, residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants may in some cases be present in pollen and some individuals (e.g., those living or working near enough to farms, nurseries or other plant-growing areas to be exposed towind-blown pollen, or visiting such areas) may be exposed, through inhalation, to the pollen. On a per person basis, the potential amounts of pollen involved in these exposures are likely to be negligible in comparison

to potential exposure through the dietary route. Residues of the pesticidal substance will not in every case be present in the pollen. When present in pollen, the residues are likely to be integrated into the tissue of the pollen grain. Pollen grains are solid, insoluble particles of sufficiently large diameter that they are filtered out in the nasopharynx or in the upper respiratory tract (Refs. 41 and 46). This exemption will not change current exposures nor affect strategies for dealing with residues that are the subject of the exemption. (Ref. 41).

iv. *Drinking water*. EPA also evaluated potential non-occupational exposures in drinking water. The substances in plants or parts of plants, including residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, are produced and used inside the living plant itself. The residues are part of the living tissue of the plant. 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 tissue (including any residues that are the subject of this exemption in the tissue) as building blocks for making their own cellular components or for fueling their own metabolisms. The residues that EPA is exempting in this action, including those identified at Unit IX.B.2., as toxic at higher concentrations, are subject to the same processes of biodegradation and decay that all biotic materials undergo. This turnover of biotic materials in nature through a process of biodegradation occurs fairly rapidly (Ref. 37). There is no indication that naturally-occurring plant biotic materials, including the residues that are the subject of this exemption, are resistant to biodegradation. Because of the fairly rapid turnover of these residues, even if they reach surface waters (through pollen dispersal or parts of the plants (leaves, fruits etc.) falling into bodies of water), they are unlikely to present anything other than a negligible exposure in drinking water drawn either from surface or ground water sources.

v. *Residential exposure*. EPA is not aware of any residential uses of plant-incorporated protectants that might result in exposure to residues that are the subject of this exemption.

7. *Sensitivities of subgroups*. EPA considered available information on the sensitivities of subgroups as it pertains to residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. In performing its assessment, the Agency considered that the diet includes all of the food items that are customarily eaten by human populations or subpopulations. As discussed in this preamble, this exemption will not affect the current pattern of exposure to residues that are the subject of this exemption. Individuals recognize and are familiar with the plant-derived food they consume, and, based on prior experience with food, individuals avoid consuming foods containing substances they know, either through personal experience or through acquired knowledge, cause them problems (Refs. 8, 39, and 40). Because the exposure pattern will not be affected by publication of this exemption, the efficacy of the current strategy whereby sensitive individuals recognize and avoid foods known to cause them problems will not be affected by this exemption (Ref. 39, 40). For example, the ability of persons who have the Mediterranean form of the inherited G6PD deficiency to deal with their disease by avoiding (i.e., not consuming) fava beans will not be affected. Thus, no subgroup should be adversely affected by the exemption.

8. *Estrogenic or other endocrine effects*. While there is some information on estrogenic effects from exposure to certain pesticides, the data are limited. It is known that certain food plants (e.g., soybeans) contain estrogen mimics, termed phytoestrogens. Such phytoestrogens are currently being consumed by humans in food derived from plants and are part of the extensive history of safe human consumption of food from plants. Although no information was submitted to EPA on this issue despite the Agency specifically soliciting it in the May 16, 1997, supplemental document (62 FR 27132), EPA cannot rule out the possibility that such phytoestrogens could be used as plant-incorporated protectants. Potential exposure of humans via consumption of plant tissue to phytoestrogens exerting estrogenic effects and used as plant-incorporated protectants may need to be considered as EPA examines the issue of endocrine disruptors. If dietary exposure to phytoestrogens (that are also plant-incorporated protectants) is discovered to be a significant factor, the Agency will re-examine this exemption from the requirement of a tolerance in light of that information.

9. *Safety factors*. EPA did not rely solely on available animal data in reaching its determination that residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants can be exempted from the requirement of a tolerance. There is a long history of safe human consumption of food containing residues that are the subject of this exemption, and of food derived from animals that consume forage and other crops containing these residues (e.g., corn and other grains). EPA thus was able to rely on epidemiological studies on humans, nutritional assessments with human volunteers and animal model testing generated through a century of systematic scientific study and available in the public literature (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19). EPA also relied on knowledge from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry (including studies on plant constituents) and plant breeding. EPA believes that long-term evidence of human consumption and the large base of scientific data generated by epidemiological studies on humans and nutritional assessments with human volunteers, with a more limited reliance on animal experimentation data, is the appropriate information for evaluating whether residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants warrant exemption. Because EPA was able to rely on data from humans, the Agency concluded that a safety factor designed to account for uncertainties in extrapolating from animal data would not be necessary. In addition, because the available epidemiological and other information generated on humans was based on studies employing very large numbers of individuals, the Agency concluded that a ten-fold safety factor to account for uncertainties in analyzing the human data would not be necessary.

10. *Infants and children*. EPA considered available information on consumption patterns of infants and children, including special sensitivity, cumulative effects of residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants with other substances that may have a common mechanism of toxicity with these residues, and the need for a margin of safety for infants and children.

i. *Dietary consumption patterns*. EPA considered available information on the dietary consumption pattern of infants and children as pertains to residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. 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 milk products for nutrition, although some infants are fed

soy-based products. Soy-based products may contain residues that are the subject of this exemption. Infants begin as early as four months of age to consume specific types of solid foods from plants that may contain residues that are the subject of this exemption. Subsequent to four months of age, apart from processing to facilitate swallowing, the diets of infants begin to be based on foods consumed by the general adult population albeit in different proportions. 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 changes to more closely resemble an adult diet. The substances that are the subject of this exemption occur in the normal diet. They have been consumed by infants and children over very long periods of time and currently are being consumed by infants and children. Exposure as part of a normal diet to these substances is highly unlikely to lead to harm to infants and children. As the diets of humans change from infancy through childhood and into adulthood, there is some possibility that the amount of the substances that are the subject of this exemption being consumed may change with those consuming the greatest amounts of food of plant origin receiving the highest exposure to substances that are the subject of this exemption. There is no evidence that such changes are likely to result in disproportionately high consumption of these residues in comparison to the general population. The evidence strongly suggests that consumption of foods containing the substances that are the subject of this exemption, 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, is highly unlikely to lead to any harm.

ii. *Special susceptibility*. EPA considered available information on the potential for special susceptibility of infants and children, including prenatal and postnatal toxicity, to residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. The substances that are the subject of this exemption occur in the normal diet, and there is no evidence that exposure to such residues, as components of food, present a different level of dietary risk for infants and children, in light of neurological differences between infants and children and adults, than they would present for the adult population.

iii. *Cumulative effects of residues with other substances with a common mechanism of toxicity*. EPA examined the available information on the cumulative effect of residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants as well as other substances in food that may have a common mechanism of toxicity with these residues. The Agency's consideration of the effects of the residues that are the subject of this exemption, and other substances that have a common mechanism of toxicity, in Unit IX.B.5. and Unit IX.B.6., included consideration of effects on infants and children.

iv. *Margin of safety*. In determining whether the residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants are safe, FFDCA section 408(b)(2)(C) directs EPA in the case of threshold effects to apply a tenfold margin of safety for the residues and other sources of exposure to infants and children to account for potential prenatal and postnatal toxicity and completeness of data effects with respect to exposure and toxicity to infants and children, unless a different margin will be safe (21 U.S.C. 346a(b)(2)(C)). For residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants, EPA has determined that a tenfold margin of safety is not necessary to protect infants and children. EPA reaches this determination based on valid, complete and reliable information. EPA based its assessment of exposure and toxicity upon the information base described in Unit IX.A. and Unit IX.B.1. (Refs. 8, 11, 12, 13, 14, 15, 16, 17, 18, and 19) that arose through the long history of human consumption of food containing substances which are the subject of this exemption, and other animals that consume plants containing these substances, and other substances in food that may have a common mechanism of toxicity (Ref. 8). EPA also relied upon knowledge from the disciplines of plant genetics, plant physiology, phytopathology, microbial ecology, ecology, biochemistry (including the constituents of food) and plant breeding. Based on all of this information, EPA concludes that it is unlikely that consumption of food containing residues that are the subject of this exemption, 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, would lead to any harm. Thus, EPA has concluded that consumption of food containing residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants is safe for infants and children, and that a margin of safety need not be applied for these residues in food.

11. *Analytical methods*. EPA has decided that there is no need to employ a practical method for detecting and measuring the levels of most of the substances in plants that might be used as plant-incorporated protectants and thus might be residues of plant-incorporated protectants derived through conventional breeding from sexually compatible plants. It is not anticipated that these substances would cause adverse effects. EPA has identified nine substances of plant origin that are found in plants that are part of the normal American diet and if present at high levels can present toxic effects. These are discussed in Unit IX.B.2. Practical methods exist for detecting and measuring the concentration of these substances in food (Ref. 22). EPA consulted with the Department of Health and Human Services (DHHS) in developing the proposed exemption and in issuing this final rule.

C. Determination of Safety for United States Population, and Infants and Children

Based on the information discussed in this document today and that discussed in the 1994 **Federal Register** documents and the supplemental documents and the associated record as described in Unit X., EPA concludes that there is a reasonable certainty that no harm will result to the United States population in general, and infants and children in the United States, from aggregate exposure to any residues of the pesticidal substance portion, or inert ingredients, of plant-incorporated protectants derived through conventional breeding from plants sexually compatible with the recipient plant, including all anticipated dietary exposures and all other exposures for which there is reliable information. This finding is based on extensive use and experience, and the large associated literature on epidemiological studies, nutritional assessments with human volunteers and animal model testing of foods from plant varieties developed by moving traits among plants in sexually compatible populations. This information shows that adverse effects due to aggregate exposure through the dietary, non-food oral, dermal and inhalation routes are highly unlikely for pesticidal substances, or inert ingredients, derived through

conventional breeding from plants sexually compatible with the recipient plant. And in the unlikely event such adverse effects do occur, EPA has implemented mechanisms to ensure that it will be notified, and that FDA will be able to seize the adulterated food; i.e., the adverse effects reporting requirement at 40 CFR 174.71 and the condition limiting this exemption at § 174.479.

X. Documents in the Official Record

As indicated in Unit I.B.2., the official record for this rule has been established under docket control number OPP–300368B, the public version of which is available for inspection as specified in Unit I.B.2.

A. References

The following books, articles and reports were used in preparing this final rule and were cited in this document by the number indicated:

1. Whittaker, R. H. 1969. New concepts of kingdoms of organisms. Science, 163:150–160.

2. Environmental Protection Agency. 2000. Summary of public comments and EPA responses on issues associated with plant-incorporated protectants (formerly plant-pesticides) for docket OPP–300368 and OPP–300368A.

3. Hanson, M., and J. Halloran. In a letter dated February 22, 1995 on dockets OPP–300367 through OPP–300371.

4. Goldburg, R. In a letter dated February 6, 1995 on dockets OPP–300367 through OPP–300371.

5. Rissler, J., and M. Mellon. In a letter dated January 23, 1995 on dockets OPP–300367 through OPP–300371.

6. Environmental Protection Agency. 1994. Joint meeting of the FIFRA Scientific Advisory Panel (SAP); Subpanel on plant-pesticides, and the EPA Biotechnology Science Advisory Committee (BSAC); Subcommittee on plant-pesticides. January 21, 1994. Final Report.

7. Raven, P. H., R. F. Evert, and S. E. Eichhorn. 1992. Biology of Plants. Fifth Edition. Worth Publishers, New York, New York.

8. International Food Biotechnology Council. 1990. Biotechnologies and food; Assuring the safety of foods produced by genetic modification. In: Regulatory Toxicology and Pharmacology. Vol 12. Academic Press, New York, New York.

9. Wilks, H. M., A. Cortes, D. C. Emery, D. J. Halsall, A. R. Clarke and J. J. Holbrook. 1992. Opportunities and limits in creating new enzymes. In: Enzyme Engineering XI. Edited by D. S. Clark and D. A. Estell. Annals of the New York Academy of Sciences. Vol. 672. The New York Academy of Sciences. New York, New York.

10. Environmental Protection Agency. Meeting of the EPA Biotechnology Science Advisory Committee (BSAC); Subcommittee on plant-pesticides. July 13, 1993. Final Report.

11. World Cancer Research Fund and American Institute for Cancer Research. 1997. Food, Nutrition and the Prevention of Cancer: A Global Perspective. BANTA Book Group, Menasha, Wisconsin.

12. Lampe, J. M. 1999. Health effects of vegetables and fruit: assessing mechanisms of action in human experimental studies. *American Journal of Clinical Nutrition*. Sep;70(3 Suppl):475S–490S.

13. Ogomoto, I. A. Shibata and K. Fukuda. 2000. World Cancer ResearchFund/American Institute of Cancer Research 1997 recommendation: applicability to digestive tract cancer in Japan. Cancer Causes Control Jan;11(1):9–23.

14. Joseph, J. A., B. Shukitt-Hale, N. A. Denisova, D. Bielinski, A. Martin, J. J. McEwen and P. C. Bickford. 1999. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation.*Journal of Neuroscience.* Sep 15;19(18):8114–21.

15. Segasothy, M. and P. A. Phillips. 1999. Vegetarian diet: panacea for modern lifestyle diseases? *QJM Monthly Journal of the Association of Physicians*. Sep;92(9):531–44.

16. Joshipura, K. J., A. Ascherio, J. E. Manson, M. J. Stampfer, E. B. Rimm, F. E. Speizer, C. H. Hennekens, D. Spiegelman and W. C. Willett. 1999. Fruit and vegetable intake in relation to risk of ischemic stroke. *Journal of the American Medical Association*. Oct6;282(13)1233–9.

17. Thompson, H. J., J. Heimendinger, A. Haegele, S. M. Sedlacek, C. Gillette, C. O'Neill, P. Wolfe and C. Conry. 1999. Effect of increased vegetable and fruit consumption on markers of oxidative cellular damage. *Carcinogenesis*. Dec;20(12):2261–6.

18. New, S. A., S. P. Robins, M. K. Campbell, J. C. Martin, M. J. Garton, C. Boltin-Smith, D. A. Grubb, S. J. Lee and D. M. Reid. 2000. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health?*American Journal of Clinical Nutrition*. Jan;71(1):142–51.

19. Michaud, D. S., D. Spiegelman, S. K. Clinton, E. B. Rimm, W. C. Willett and E. L. Giovannucci. 1999. Fruit and vegetable intake and incidence of bladder cancer in a male prospective cohort. *Journal of the National Cancer Institute*. Apr7;91(7):605–13.

20. Environmental Protection Agency issue paper. 1994. FIFRA: Benefit and environmental risk considerations for inherent plant-pesticides.

21. Agrios, George. 1988. Plant Pathology. Third Edition. Academic Press. New York, New York.

22. Environmental Protection Agency issue paper. 2000. Natural toxicants in food.

23. USDA Agricultural Research Service Poisonous Plant Research Laboratory. Bulletin 415: Poisonous plants of the western United States: Neurotoxic and mycotoxic plants. [http://www.pprl.usu.edu/bulletin.htm]

24. Hernando, J. E. and J. Leon (eds) Neglected Crops: 1492 from a different perspective. FAO Plant production and protection series No. 26. Rome Italy, p. 131–148. 1994.

25. Shibamoto, T. And L.F. Bjeldanes. 1993. Introduction to Food Toxicology. Academic Press, Inc. San Diego, New York, Boston.

26. Ellenhorn, M. J. S. Schonwald, G. Ordog and J. Wasserberger. 1997. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Second Edition. Williams and Wilkins. Baltimore, MD

27. Cooper, R. A., and H. F. Bunn. Hemolytic anemias. 1980. In: Harrison's Principles of Internal Medicine. Edited by. K. J. Isselbacher, R. D. Adams, E. Braunwald, R. G. Petersdorf and J. D. Wilson. McGraw-Hill Company.

28. Coulston, F., and A. C. Kolbye. 1990. (Eds) Regulatory Toxicology and Pharmacology. 12(3), S20–S30.

29. Concon, J. M. 1988. Food Toxicology: Principles and Concepts. Marcel Decker Inc. New York and Basel.

30. Environmental Protection Agency issue paper. 2000. The glycoalkaloid class; solanine and chaconine: Mechanisms of action.

31. D'Mello, J. P. F. 1997. Handbook of Plant and Fungal Toxicants. CBC Press. Boca Raton, New York.

32. Tice, R. 1998. Chacoline and solanine: Review of the Toxicological Literature. Prepared for E. Zeiger, National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health. [http://ntp-server.niehs.nih.gov/htd. ...und/ExecSumm/ ChaconineSolanine.html

33. Environmental Protection Agency. 2000. Benefits of fruits and vegetables.

34. Taylor, P. 1996. Anticholinesterase agents. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. Ninth Edition. Edited by J. G. Hardman, L. E. Limbird,

P. B. Molinoff, and R. W. Rudden. McGraw-Hill Health Profession Division. New York, New York.

35. Baker, D. C., R. F. Keeler, and W. P. Gaffield. 1988. Mechanism of death in syrian hamsters gavaged potato sprout material. Toxicologic Pathology. Vol. 16:333

36. Environmental Protection Agency. 1999. Guidance for identifying pesticide chemicals and other substances that have a common mechanism of toxicity. FAX-on-Demand Number : (202) 401–0527. Item: 6055.

37. Atlas, R. and R. Bartha. 1987. Microbial Ecology. Benjamin/Cummings Publishing Company, Inc. Menlo Park, California.

38. National Research Council. 1999. Hormonally Active Agents in the Environment. National Academy Press. Washington DC.

39. Yunginger, J. W. 1991. Food Antigens. In: Food Allergy: Adverse Reactions to Foods and Food Additives. Edited by D. D. Metcalfe, H. A. Sampson, and R. A. Simon. Blackwell Scientific Publications. Cambridge, Massachusetts.

40. O'Mahony, S. And A. Ferguson. 1991. Gluten-Sensitive Enteropathy (Celiac Disease). In: Food Allergy: Adverse Reactions to Foods and Food Additives. Edited by D. D. Metcalfe, H. A. Sampson, and R. A. Simon. Blackwell Scientific Publications. Cambridge, Massachusetts.

41. Environmental Protection Agency issue paper. 2000. Dermal and inhalation exposure to plant substances.

42. Lovell, C. R. 1993. Plants and the skin. First edition. Oxford, Blackwell Scientific Publications.

43. Guy, R. H., and J. Hadgraft. 1991. Principles of skin permeability relevant to chemical exposure. In: Dermal and Ocular Toxicology: Fundamentals and Methods. Edited by D. W. Hobson. CRC Press Boca Raton, Florida.

44. Murray, M. T. 1995. The Healing Power of Herbs. Prima Publishing, Rocklin, California.

45. Glinsukon, T., Stitmunnaithum, V., Toskulkao, C., Buranawuti, T., and V. Tangkrisanavinont. Acute toxicity of capsaicin in several animal species. *Toxicon.* 18(2):215–20. 1980.

46. Environmental Protection Agency. 1997. Exposure Factors Handbook. Volume 1. National Center for Environmental Assessment. EPA/600/P–95/002Fa.

47. Environmental Protection Agency. 2000. Economic analysis of the plant-incorporated protectant regulations under the Federal Insecticide, Fungicide, and Rodenticide Act.

B. Additional Information

The complete official record for this rulemaking includes:

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

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

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

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

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

The docket identified by the docket control number OPP–300370A for the document entitled ''Plant-Pesticide Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act; Reopening of Comment Period'' (61 FR 37891, July 22, 1996) (FRL–5387–4).

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

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

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

The docket identified by the docket control number OPP–30069A for the document entitled ''Plant-Pesticides, Supplemental Notice of Availability of Information'' (64 FR 19958, April 23, 1999) (FRL–6077–6).

The docket identified by the docket control number OPP–300371B for the companion 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)'' (FRL–6057–5) published elsewhere in this issue of the **Federal Register**.

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)'' (FRL–6057–7)published elsewhere in this issue of the **Federal Register**.

The docket identified by the docket control number OPP–300368B for this document (FRL–6057–6).

Also include in the complete official public record are:

1. Public comments submitted in response to the proposals and supplemental documents cited in this Unit X.B.

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

3. The Economic Analysis (EA) for the final rule on FIFRA regulations for plant-incorporated protectants, and documents supporting the EA (Ref. 47).

4. Support documents and reports.

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

6. Published literature that is cited in this document.

7. The response to comments document pertaining to the development of this final rule (Ref. 2).

XI. Regulatory Assessment Requirements

This final rule establishes an exemption from the tolerance requirement under FFDCA section 408 and does not impose any other regulatory requirements. As such, The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive

Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993).

This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, nor does it require OMB review or any Agency action under Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997).

This action does not 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), nor does it 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), Public Law 104–113, section 12(d) (15 U.S.C. 272 note).

This action does not impose any enforceable duty or contain any unfunded mandate, and will not otherwise significantly or uniquely affect small governments as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104–4). This rule does not significantly or uniquely affect the communities of Indian trial governments, nor does it involve or impose any requirements that affect Indian Tribes. Accordingly, the requirements of section 3(b) of Executive Order 13084, entitled *Consultation and Coordination with Indian Tribal Governments* (63 FR 27655, May 19, 1998), do not apply to this rule. Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000), which took effect on January 6, 2001, revokes Executive Order 13084 as of that date. EPA developed this rulemaking, however, during the period when Executive Order 13084 was in effect; thus, EPA addressed tribal considerations under Executive Order 13084. For the same reasons stated for Executive Order 13084, the requirements of Executive Order 13175 do not apply to this rule either. For the same reasons, this rule does not have any substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999). This rule directly regulates growers, food processors, food handlers and food retailers, not States. This action does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4).

Pursuant to section 605(b) of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), the Agency hereby certifies that this final rule will not have a significant economic impact on a substantial number of small entities. The Agency's determination is based on the fact that an exemption from the requirement of a tolerance under FFDCA section 408, such as that contained in this rule, will not adversely affect any small businesses. Additional information about the Agency's determination may be found in the small entity impact analysis prepared as part of the economic analysis for the FIFRA rulemaking, which is available in the public version of the official record under OPP–300368B (Ref. 47). The Agency has also 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 these actions. See 46 FR 24950, May 4, 1981.

This rule is not subject to Executive Order 13211, entitled *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001), because this action is not expected to affect energy supply, distribution, or use.

XII. Submission to Congress and the Comptroller General

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, as added by the Small Business Regulatory Enforcement Fairness Act of 1996, generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report, which includes a copy of the rule, to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of this final rule in the **Federal Register**. This final rule is not a ''major rule'' as defined by 5 U.S.C. 804(2).

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: July 12, 2001.

Christine T. Whitman,

Administrator.

Therefore, 40 CFR chapter I is amended as follows:

PART 174—[AMENDED]

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

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

2. Section 174.479 is added to subpart W to read as follows:

§ 174.479 Pesticidal substance from sexually compatible plant; exemption from the requirement of a tolerance.

Residues of a pesticidal substance that is part of a plant-incorporated protectant from a sexually compatible plant are exempt from the requirement of a tolerance if all the following conditions are met:

(a) The genetic material that encodes for the pesticidal substance or leads to the production of the pesticidal substance is from a plant that is sexually compatible with the recipient food plant.

(b) The genetic material has never been derived from a source that is not sexually compatible with the recipient food plant.

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

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