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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2015-0230; FRL-9998-74]

RIN 2070-ZA16

Banda de *Lupinus albus* doce (BLAD); Proposal to Revoke Exemption and Establish Pesticide Tolerances

AGENCY: Environmental Protection Agency (EPA or Agency).

ACTION: Proposed rule; reproposal.

SUMMARY: On May 29, 2015, EPA proposed to revoke the current exemption from the requirement of a tolerance for residues of banda de *Lupinus albus* doce (BLAD) in or on all food commodities and to establish tolerances for residues of BLAD in or on almonds, grapes, strawberries, and tomatoes. Following the receipt of several comments, the Agency is reproposing this action in order to clarify its proposed rulemaking. In addition, since the publication of the initial proposal, the registrant has requested that the Agency establish tolerances for additional commodities. The Agency is undertaking this action under the Federal Food, Drug, and Cosmetic Act (FFDCA).

DATES: Comments must be received on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: Submit your comments, identified by docket identification number EPA-HQ-OPP-2015-0230, by one of the following methods:

• *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is

restricted by statute.

• *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001.

• *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/where-send-comments-epa-dockets*.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Anne Overstreet, Deputy Director, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: *BPPDFRNotices@epa.gov*.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

• Crop production (NAICS code 111).

• Animal production (NAICS code 112).

• Food manufacturing (NAICS code 311).

• Pesticide manufacturing (NAICS code 32532).

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

1. *Submitting CBI*. Do not submit this information to EPA through regulations.gov or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information on a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes 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 docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments*. When preparing and submitting your comments, see the commenting tips at *http://www.epa.gov/dockets/commenting-epa-dockets#tips*.

II. This Proposal

A. What is the Authority for this Action?

EPA is taking this action under section 408(e) of the FFDCA, 21 U.S.C. 346a(e), which allows EPA to issue regulations, including establishing tolerances and revoking exemptions, on its own initiative. Under FFDCA section 408(e), the Agency applies the same standards for establishing tolerances and revoking exemptions found in FFDCA section 408(b) and (c), 21 U.S.C. 346a(b) and (c). FFDCA section 408(b)(2)(A)(i) allows EPA to establish a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is "safe." FFDCA section 408(b)(2)(A)(ii) defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is

reliable information." This includes exposure through drinking water and in residential settings but does not include occupational exposure. FFDCA section 408(b)(2)(C) requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue…."

The relevant portion of FFDCA section 408(c)(2)(A)(i) requires the Agency to modify or revoke an exemption if the Agency determines it is not safe, where "safe" has the same definition as in FFDCA section 408(b)(2)(A)(ii).

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. For further discussion of the regulatory requirements of FFDCA section 408 and a complete description of the risk assessment process, see *http://www.epa.gov/pesticide-tolerances/setting-tolerances-pesticide-residues-foods*.

B. What Action is the Agency Taking?

EPA is proposing to revoke the existing exemption from the requirement of a tolerance for residues of the fungicide BLAD in or on all food commodities that was established in the **Federal Register** of March 22, 2013 (78 FR 17600) (FRL-9380-6). In place of the exemption, EPA is proposing to establish tolerances for residues of the fungicide BLAD at the level of quantitation (LOQ), i.e., 0.02 parts per million (ppm), in or on the following commodities: almond; almond, hulls; fruit, pome, group 11-10; fruit, stone, group 12-12; grape; hops, dried cones; strawberry; vegetable, cucurbit, group 9; and vegetable, fruiting, group 8-10.

EPA is taking this action in response to concerns raised by the U.S. Food and Drug Administration (FDA) about the potential allergenicity of BLAD for lupin-sensitive and/or peanut-sensitive individuals following EPA's promulgation of the tolerance exemption of BLAD

on all food commodities. (Ref. 1). Based on the potential uncertainty raised by those concerns, EPA sought additional data from the petitioner and reexamined the safety of the BLAD tolerance exemption. Following further review of BLAD and an assessment of the additional data that were provided, EPA has concluded that given the source of BLAD and the results of bioinformatics analysis, such data do not disprove the potential for BLAD to pose an allergenicity risk to lupin-sensitive and peanut-sensitive individuals. As a result, EPA no longer considers the existing tolerance exemption for residues of BLAD, which, on its face, permits unlimited residues of BLAD in or on all food commodities, to be safe. Nevertheless, EPA concludes that the available residue data and food processing information support a safety determination for establishing numerical tolerances at the LOQ for residues of BLAD in or on almond; almond, hulls; fruit, pome, group 11-10; fruit, stone, group 12-12; grape; hops, dried cones; strawberry; vegetable, cucurbit, group 9; and vegetable, fruiting, group 8-10.

III. Guidance for Assessing Allergenicity

The Agency considered the following sources of internationally accepted guidance in assessing the potential allergenicity of BLAD. Although these documents are primarily concerned with the safety of foods that have been genetically modified, the allergenicity analysis is relevant since it outlines a process for evaluating whether the gene (or protein) engineered into the food has introduced an allergen or resulted in a food that may be allergenic. EPA considers the recommended approaches for assessing potential allergenicity to apply equally to proteins that may be applied directly onto the plant as well as those directly incorporated into the plant via genetic engineering.

A. Report of Joint FAO/WHO Expert Consultation (2001)

In 2001, the Joint Food and Agriculture Organization of the United Nations (FAO)/World

Health Organization (WHO) Expert Consultation on Allergenicity of Foods Derived from Biotechnology was held at the headquarters of the FAO. The 28-expert consultation focused on the question of allergenicity of genetically modified foods and prepared a report providing scientific advice for the assessment of allergenicity of genetically modified foods. (Ref. 2, hereinafter "2001 FAO/WHO Report"). The consultation developed a new decision tree identifying two paths for assessing allergenicity, depending upon whether the source of the gene is a known allergen. (*Id*. at 6, 26).

If the source of the gene is a known allergen, the analysis focuses on both sequence homology and specific sera testing. (*Id*. at 7-8). Determining sequence homology to a known allergen is the first step for genes derived from known allergenic sources. The 2001 FAO/WHO Report notes that significant sequence homology is indicated (and thus a potential for cross-reactivity between the new protein and a known allergen) when there is more than 35% identity between the amino acid sequence of the expressed protein and the known allergen, within a window of 80 amino acids. (*Id*. at 10-11).[1] If the sequence homology demonstrates similarity to a known allergen, the product is considered allergenic, i.e., a person sensitive to a known allergen is likely to be allergic to the new protein as well. (*Id*. at 7). The 2001 FAO/WHO Report notes that for proteins derived from known allergenic sources where sequence homology to a known allergen is demonstrated, "the product is considered allergenic, and no further testing is typically undertaken." (*Id*.)

The 2001 FAO/WHO Report provides that for proteins derived from known allergenic sources where the sequence homology analysis is negative, a specific serum screen is to be

[1] The 2001 FAO/WHO Report also recognizes that potential for cross-reactivity may require consideration of additional factors when proteins have less than 35% identity with a known allergen in a window of 80 amino acids. (Ref. 2 at 11). These considerations are not discussed in this document since the sequence homology for BLAD exceeds 35% identity with other known allergens.

conducted. (*Id*. at 7). The 2001 FAO/WHO Report recommends using only patients with a level of sensitization to the allergen source of more than 10 kilointernational units per liter (kIU/L) of specific immunoglobulin E (IgE), in order to ensure that the test is conducted with sera from patients sufficiently allergic to the source material, and cautions that patients who have a low level of sensitization may not provide useful results for assessing reactivity to the expressed protein. (*Id*.) Assuming adequately sensitive sera are available, the 2001 FAO/WHO Report notes that the degree of confidence in the results of the specific serum screening will depend upon the number of sera available for analysis. To achieve a 95% certainty that a substance is not a major allergen, a negative result must be obtained with at least 6 relevant sera; 99% certainty, at least 8 relevant sera; 99.9% certainty, at least 14 relevant sera. To achieve 95% certainty that a substance is not a minor allergen, a negative result must be obtained with at least 17 relevant sera; 99% certainty, at least 24 relevant sera. Larger numbers of sera are recommended to increase the confidence associated with negative immunoassay results; using fewer sera carries the risk of a false negative outcome. (*Id*.) The 2001 FAO/WHO Report notes that the *in vitro* method applied to assess the results should be a validated assay measuring specific IgE. (*Id*.)

The 2001 FAO/WHO Report concludes that any positive results from the sera screen will define the product as likely to be allergenic and will normally lead to discontinuation of product development. (*Id*.) A negative outcome from the sera screen does not necessarily support a conclusion that the product is not allergenic, however; rather, because of the allergenic nature of the source of the substance, a desire to continue with product development will normally prompt further analysis to rule out allergenicity concerns (i.e., targeted serum screening, analysis of pepsin resistance, and animal modeling, and in selected cases, *in vivo/ex vivo* testing (i.e., skin

prick testing, basophil histamine release, and oral challenge)). (*Id*. at 7-8).

If the source of the protein is not a known allergen, the 2001 FAO/WHO Report decision tree advises consideration of four sets of data: (1) sequence homology with known allergens; (2) targeted serum testing; (3) pepsin resistance; and (4) immunogenicity testing in animal models. (*Id*. at 8). If the sequence homology reveals a level of homology with a known allergen, the protein is "considered to be an allergenic risk … [and n]o further evaluation for allergenicity would typically be necessary." (*Id*.) If the sequence homology does not identify any similarities, the 2001 FAO/WHO Report notes that it does not necessarily mean that the substance is not an allergen. Rather, because of potential limitations in the databases or limited information on the relevant allergen, the 2001 FAO/WHO Report recommends that a targeted serum screen be conducted to test for cross-reactivity of individual serum samples containing high levels of IgE antibodies specific to a source broadly related to the source of the substance at issue, e.g., if the gene is derived from a monocot, sera from individuals with allergies to other monocots would be used in the screen. (*Id*. at 12). A positive result with one of these sera will indicate that the substance is likely to be allergenic and further study would not be necessary, unless further confirmation is sought through *in vivo/ex vivo* approaches mentioned above. (*Id*. at 8). Negative results would then lead to the analysis of the protein for pepsin resistance (i.e., how completely the protein degrades in the presence of pepsin during digestion) and evidence of immunogenicity in appropriate animal models. (*Id*. at 12-13). The 2001 FAO/WHO Report recommends that any results of these analyses be taken into consideration in combination with the rest of the decision tree criteria. (*Id*. at 13.)

B. Codex Alimentarius Guidance (2009)

The Codex Alimentarius Guidance is a "collection of internationally adopted food

standards, guidelines, codes of practice and other recommendations," developed by an intergovernmental body with more than 180 members, within the framework of the Joint Food Standards Programme established by the FAO and WHO. (Ref. 3, preface). Contained within the Codex Alimentarius Guidance, the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants ("Codex Guideline") addresses safety and nutritional aspects of genetically altered foods and recommends an approach for assessing the safety of foods derived from recombinant-DNA plants and plants altered by other techniques. (*Id*. at 7-33).

The Codex Guideline states that all newly expressed proteins in recombinant-DNA plants should be assessed for their potential to cause allergic reactions. (*Id*. at 15). The Codex Guideline describes stepwise approach to the assessment of the possible allergenicity of newly expressed proteins. (*Id*. at 20-23). The initial assessment involves three steps: (1) identify the source of the protein; (2) assess the extent to which a protein is similar in structure to a known allergen; and (3) evaluate the resistance of the protein to degradation by pepsin. (*Id*. at 21-22).

The Codex Guideline states that "[i]t is important to establish whether the source is known to cause allergic reactions. Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise." (*Id*. at 21). The Codex Guideline notes "[t]he transfer of genes from commonly allergenic foods … should be avoided unless it is documented that the transferred gene does not code for an allergen…." (*Id*. at 15). Because there is no single definitive test for predicting allergic human response, "[k]nowledge of the source of the introduced protein allows the identification of tools and relevant data to be considered in the allergenicity assessment. These include: the availability of sera for screening purposes; documented type, severity and frequency of allergic reactions;

structural characteristics and amino acid sequence; physicochemical and immunological properties (when available) of known allergenic proteins from that source." (*Id*. at 21).

The next piece of the allergenicity assessment is the amino acid sequence homology, the purpose of which is to determine whether a protein is similar in structure to a known allergen and thus has allergenic potential. (*Id*.) Assessing similarity to known allergens is done by comparing the new protein to databases of known allergens, looking for two types of similarity. First, the sequence homology looks for contiguous identical amino acid segments; the Codex Guideline noted that "the size of the contiguous amino acid search should be based on scientifically justified rationale in order to minimize the potential for false negative or false positive results," whereas the 2001 FAO/WHO Report recommended moving from 8 to 6 identical amino acid segments. (*Id*.) Second, the sequence homology looks for whether there is a potential for human IgE cross-reactivity between the new protein and a known allergen. (*Id*.) The Codex Guideline incorporates the finding of the 2001 FAO/WHO Report, which concludes that a potential cross-reactivity is likely when there is more than 35% identity in a segment of 80 or more amino acids. (*Id*.) Where there is a negative sequence homology, it indicates that the protein is not a known allergen and is unlikely to be cross-reactive with known allergens. (*Id*. at 22). A positive sequence homology indicates that the protein is likely to be allergenic and, in order to be considered further, specific serum testing (i.e., testing conducted using serum of individuals who are sensitized to the allergenic source) should be conducted. (*Id*.)

The Codex Guideline also recognizes that many food allergens exhibit resistance to pepsin digestion and thus resistance to pepsin digestion can be used to assess potential allergenicity. (*Id*.) If a protein is resistant to pepsin digestion, it suggests that further analysis should be conducted to evaluate potential allergenicity; however, the Codex Guideline notes that

lack of resistance does not necessarily mean that the protein is not an allergen. (*Id*.)

The Codex Guideline states that for proteins that originate from a known allergenic source or that have sequence homology with a known allergen, testing in immunological assays should be performed where sera are available. (*Id*.) The sera should be obtained from individuals with a "clinically validated allergy" to the protein source, and sera must be obtained from sufficient numbers of individuals to achieve the necessary level of confidence in the test results regarding the protein's allergenicity. (*Id*.) The 2001 FAO/WHO Report notes that, in the case of a major allergen, a minimum of eight relevant sera is required in order to achieve a 99% certainty that the new protein is not an allergen, while in the case of a minor allergen, a minimum of 24 is required. (*Id*. at n.11). In addition, the "quality of the sera and the assay procedure need to be standardized to produce a valid test result." (*Id*. at 23). "[A] negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols. A positive result in such tests would indicate a potential allergen." (*Id*.)

IV. Regulatory Background

BLAD is a protein fragment with fungicidal properties. More specifically, BLAD is a 20 kilodalton (kDa) polypeptide fragment of β-conglutin, a main storage protein in the flowering plant sweet lupin (*Lupinus albus*). BLAD is produced by breakdown of β-conglutin during day 4 to 12 of the germination process of sweet lupins. BLAD degrades chitin by catalyzing and successfully removing the N-acetyl-D-glucosamine terminal monomers, resulting in the destruction of fungal cells. (Ref. 4).

In the **Federal Register** of March 22, 2013 (78 FR 17600) (FRL-9380-6), EPA established an exemption from the requirement of a tolerance for residues of BLAD in or on all

food commodities when applied as a fungicide and used in accordance with label directions and good agricultural practices. EPA established this tolerance exemption following the receipt of a petition from Consumo Em Verde S.A., Biotecnologia De Plantas, Parque Technologico de Cantanhede (CEV) in 2012. The Agency's safety finding was based on an assessment of available data and an assumption that there was a long history of safe use in human and animal consumption without any adverse effects.

Although the preamble to the March 2013 final rule did not discuss the potential allergenicity of BLAD, EPA's supporting memorandum for the establishment of a tolerance exemption examined BLAD's potential allergenicity, based on the available information EPA had about BLAD at the time. (Ref. 4). Observing that (i) BLAD comprises an internal segment of β-conglutin, (ii) β-conglutin exhibits a relatively strong homology to the other members of the vicilin family, including well-known allergens contained in peanuts and soybeans, and (iii) there were a considerable number of studies concerning the allergenicity of lupin-derived products, EPA conducted an allergenicity assessment of BLAD. (*Id*.) EPA examined BLAD under the criteria in the 2001 FAO/WHO Report and the Codex Guideline for assessing proteins not known to be derived from an allergenic source, which it characterized as follows: (la) amino acid residue homology >35%, or (1b) identity in one or more sets of >6 contiguous amino acid residues, or (1c) cross-reactivity to known allergens; (2) high resistance to proteolytic attack; and (3) ingestion of sufficient amounts. (*Id*.) Although EPA found that BLAD exhibited a high sequence homology with a well-established peanut allergen, Ara h 1, EPA concluded that a tolerance exemption would be safe because, when used according to the proposed label directions, BLAD's potential exposure and harmful effects to humans would be negligible, and no adverse effects such as allergenic reactions would be expected. (*Id*.)

Following EPA's establishment of this BLAD tolerance exemption, however, FDA expressed concerns about the potential allergenicity of BLAD for lupin-sensitive and/or peanut-sensitive individuals. (Ref. 1). FDA noted that the preamble to the March 2013 final rule did not discuss allergenicity and disagreed with EPA's statement in the tolerance exemption preamble about the long history of safe consumption of sweet lupins. (*Id*.) FDA noted that BLAD is derived from the lupin plant and provided information concerning the allergenicity of lupin. (*Id*.) Specifically, FDA provided scientific literature indicating that lupin causes allergic reactions and epidemiological evidence indicating that lupin is an increasingly significant allergenic hazard in Europe where it is consumed. (*Id*.) FDA also referred EPA to the 2005 European Food Safety Authority (EFSA) official opinion. The EFSA opinion examined the potential for allergenicity of lupin in response to a request from the European Commission, which was considering whether to place lupin on a list of known allergens and require lupin identification on food labels. (*Id*.; see also Ref. 5). The EFSA opinion noted allergic reactions to lupin have been documented in individuals allergic to peanuts and those with no known allergy to peanuts. (Ref. 5).

FDA also provided information on BLAD's bioinformatics. Using publicly available sequence information, FDA determined that β-conglutin, the specific protein from which BLAD is derived, is a major lupin allergen, Lup an 1. (Ref. 1). FDA further concluded that BLAD has a high amino acid sequence identity to two major allergens—Lup an 1 and Ara h 1, a major peanut allergen. (*Id*.) Based on information about the allergenicity of the source plant and the sequence homology to major allergens, FDA concluded that, under the Codex Guideline and the 2001 FAO/WHO Report, BLAD would be considered an allergen until proven otherwise. (*Id*.)

Taking this new information concerning BLAD's source into account along with

BLAD's bioinformatics, EPA proceeded to analyze BLAD under the Codex Guideline approach for assessing proteins derived from known allergenic sources, which emphasizes the need for specific sera testing to overcome the presumption that the protein will be allergenic. (Ref. 6). This new approach differed from the approach EPA used in its initial assessment of BLAD; lacking information that the protein was derived from a known allergenic source, EPA had used the general assessment approach recommended for proteins that are not known to be derived from known allergenic sources. (*Id*.) In addition to using this new approach, EPA sought FDA's insight on evaluating food allergens as it evaluated BLAD's potential allergenicity.

Applying the 2001 FAO/WHO Report and Codex Guideline processes for assessing substances derived from known allergenic sources, EPA requested that CEV submit additional data to overcome the presumption that BLAD would pose a potential allergenicity concern. EPA also required residue chemistry field trials and a residue decline study to determine likely residue levels of BLAD on treated commodities listed on the pesticide label. (*Id*.) Upon receipt of this new information, EPA reexamined the safety of BLAD.

Based on that reexamination, on May 29, 2015, EPA proposed to revoke the established tolerance exemption, which, on its face, contains no numerical limit on permissible residues in or on all food commodities, and to establish tolerances for residues of BLAD in or on almonds, grapes, strawberries, and tomatoes at 0.005 ppm (the level of detection). 80 FR 30640 (May 29, 2015). In essence, the proposal noted that, since the available allergenicity data did not rule out the potential of BLAD's allergenicity, the Agency was unable to continue supporting the safety finding for the BLAD exemption, which set no numerical limits for exposures to BLAD on all food commodities, which facilitate the process for identifying residues that might be higher than expected in instances of pesticidal misuse. Nevertheless, the Agency determined that, because

the available residue data indicate a lack of detectable residues on certain commodities (i.e., almonds, grapes, strawberries, and tomatoes), numerical tolerances set at the level of detection for ensuring negligible residues of BLAD on almonds, grapes, strawberries, and tomatoes as expected under approved label use conditions were safe. *Id*. at 30643-44.

The Agency received five timely comments on the proposal, as well as a number of late-filed comments. Of those timely comments, many expressed confusion about the Agency's basis for its proposal and challenged whether the proposal was based on the available data. Some commenters also expressed concerns for the proposal's impact on farmers and trade. Upon further review of that proposal and following additional consultation with FDA regarding the commenters' scientific challenges to the proposal (Refs. 7, 8), the Agency recognized that the rationale for its May 29, 2015, proposal could have been presented more clearly. In addition, the registrant requested that additional commodities be added to this tolerance rulemaking action. Consequently, in response to the concerns raised in the comments and the request for additional commodities, the Agency has decided to repropose with additional explanation addressing the basis for revoking the tolerance exemption and establishing tolerances set at the LOQ for residues in or on the commodities identified in the May 29, 2015, proposal, as well as other commodities requested by the registrant in the interim. This reproposal supersedes and replaces the proposal issued on May 29, 2015.

V. Aggregate Risk Assessment and Determination of Safety

A. Toxicological Profile

EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major

identifiable subgroups of consumers, including infants and children.

As noted in the preamble to the March 22, 2013, final rule, all of the toxicity data requirements have been fulfilled. The toxicological profile of BLAD has not changed since that rule; therefore, EPA is relying on the toxicity findings in that document and supporting documents to support its continuing conclusion that BLAD does not present any toxic concerns. 78 FR at 17601-02 and Ref. 4.

As noted in Unit IV., upon receiving new information about BLAD's source from FDA, EPA reexamined the potential allergenicity of BLAD for lupin-sensitive and peanut-sensitive individuals, using the approach recommended in the 2001 FAO/WHO Report and in the Codex Guideline: (1) identify the source of the protein; (2) assess the extent to which a protein is similar in structure to a known allergen; and (3) for substances derived from a known allergenic source and that have sequence homology with a known allergen, test sera of a sufficient number of individuals who are sensitized to the allergenic source. (Refs. 2, 3).

BLAD is a fragment of the β-conglutin protein produced in the sweet lupin (*Lupinus albus*). There are several sources indicating that lupin is a major allergen. First, EFSA has issued a number of science opinions recognizing lupin as causing allergic reactions in peanut-sensitive individuals and IgE sensitization in individuals with no known allergy to peanuts. (Refs. 5, 9). Based on the EFSA reports, the European Commission added lupin to the list of major allergens that must be identified on food labels. (Ref. 10). FDA also considers lupin to be a food allergen and, based on reports of allergic reactions to lupin (some severe), has issued advisory statements to alert consumers to the potential for allergic reactions to foods containing lupin, especially those individuals with a peanut allergy. (Refs. 8, 11, 12). In addition, both EFSA and FDA cite to extensive scientific literature indicating that exposure to lupin causes

allergic reactions in peanut-sensitive individuals (indicating cross-reactivity), as well as in the general population. (Refs. 1, 5, 8). After considering this information, EPA has concluded that lupin, from which BLAD is derived, is a known allergen.

EPA also assessed BLAD for any sequence homology to known allergens. EPA determined that BLAD exhibits a high sequence homology (58%) when compared to Ara h 1, a recognized allergen known for causing allergic reactions (sometimes severe) in peanut-sensitive individuals. (Ref. 4). In addition, FDA informed EPA that BLAD is also 86% identical and 91% similar in amino acid sequence (with no gaps) to Lup an 1.0101, the β-conglutin derived from *Lupinus angustifolius*. (Ref. 8). Lup an 1 has been recognized as a food allergen in the World Health Organization/International Union of Immunological Sciences database, (Ref. 13), and EFSA considers Lup an 1 to be the major lupin allergen. (Ref. 9 at 165). Given that BLAD is derived from a known allergen and has a high sequence homology to two known allergens, EPA required additional testing to further assess BLAD's potential allergenicity, consistent with the Codex Guideline recommendation to seek specific serum testing or immunological assays where sera are available.

In response, CEV agreed to conduct studies that test for allergenicity, including a skin prick (*in vivo*) test on individuals sensitive to Ara h 1 and *in vitro* immunological testing on serum from those individuals. (Ref. 14). After identifying several patients who reported having an allergy, a skin prick test (SPT) was conducted in order to establish a sampling population that was sensitive to lupins and/or peanuts. (Ref. 15). Sera from 30 individuals[2] who were found in the SPT to have a sensitivity to the lupin and/or peanut extract were used to evaluate the capacity of cross-reactivity to BLAD in these sensitive individuals. (Ref. 6). The IgE-specific *in vitro*

[2] The initial serum study selected 26 patients who reacted to the lupin and/or peanut in the SPT. After EPA expressed concern about some of the results of the study, sera from additional patients were included in the study. (Refs. 6, 15).

immunoblot (ELISA) testing results did not indicate any IgE binding to BLAD, i.e., the results indicated that BLAD did not react with the tested patients' sera. (*Id*.; Ref. 15).

While the lack of reactivity indicates that BLAD may not cause an allergic response in the tested patients, EPA has determined, as discussed below, that this study is not sufficient to overcome the presumption of allergenicity for BLAD among the general population of lupin-sensitive and/or peanut-sensitive individuals, given the protein's source and sequence homology. (Ref. 16). As noted in Unit III.B., according to the Codex Guideline, "a negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols." (Ref. 3 at 23). The critical issues are the availability of sera from a sufficient number of individuals, the quality of the sera, and the standardization of the assay procedure. (*Id*. at 22-23.)

Both EPA and FDA have reviewed the submitted data to determine whether it supports a conclusion that BLAD is not an allergen. Because of FDA's initial concerns about BLAD and in light of FDA's experience evaluating food allergens, EPA discussed the submitted data with FDA and considered FDA's analysis of the sera testing in EPA's own assessment of the data. FDA identified several concerns about the sufficiency of the quantity and quality of the sera used in the testing, which raise questions about the scientific reliability of the data for proving that BLAD is not an allergen. As an initial matter, FDA noted that the sera testing method "is not the most robust for disproving allergenicity to a potential allergenic food ingredient." (Ref. 8 at 4-5). FDA explained that the "most reliable or 'gold standard' method for assessing whether or not a food or food protein will be clinically reactive is clinical testing by oral food challenge in a well-characterized group of food allergic individuals." (*Id*. at 5). One of FDA's concerns about the serum test itself relates to the level of characterization of the recruited patients' clinical

history. (*Id*.) FDA notes that it typically encourages submitters of *in vitro* sera testing to test a "statistically significant number of sera from well-characterized food allergic individuals." (*Id*.) In reviewing the BLAD sera study, FDA found such characterization lacking, in that characterization consisted of recruited patients' own clinical history of reactions to lupin or peanut and a skin prick test. (*Id*.) FDA further explained why this level of clinical history characterization raises uncertainty about whether sera were obtained from an appropriately sensitive population of allergic individuals:

[W]ithout confirmation of allergy by observed positive food allergen challenge, there remain uncertainties about how truly reactive these patients are to the food allergen and how representative they are of the population of potential reactors to the allergen. For example, depending on when the last allergic reactions occurred, a patient may have outgrown their food allergy yet still be sensitized (having specific IgE) to the allergen. Also, some subjects may have associated non-specific reactions, e.g., an outbreak of hives/urticaria, to a food they had eaten or were sensitized to, even though they are not truly reactive to the food. Skin prick tests are also prone to false positive results, especially with findings of small wheal and flare responses (<4 mm) (Bernstein et al., 2008), which were the findings seen in a number of patients in the applicant's study. Inclusion of patients who are not validated to be clinically reactive to the allergen in question impacts the robustness and statistical power of the data. In the applicant's study, FDA found poorly characterized information about the recruited patients' reaction histories. (*Id*. at 5-6).

In addition, FDA expressed a concern about the level of IgE response in the recruited patients:

In addition, IgE-specific level responses to lupin and/or peanut were not found to be

robust in most patients, with levels reported to be low (less than 2 kU/L) in the majority of subjects. In clinical practice to determine if a patient with mild or unclear allergic-type symptoms to the food is allergic, most specialists would consider food challenge for a patient with peanut IgE levels less than 2 kU/L, as 50% of peanut-allergic individuals with a median measurement of 2 kU/L are reported to have negative challenges (Nowak-Wegrzyn et al., 2009; Perry et al., 2004). Although patients could still be clinically allergic at low levels of IgE, for peanut, universally accepted clinical cut-off IgE levels to predict likely clinical peanut allergy have been reported at much higher levels, i.e., 14 to 15 kU/L. Patients with specific IgE at or above these predictive levels of 14 to 15 kU/L have a 90–95% likelihood of reacting to peanut during peanut challenge (Nowak-Wegrzyn et al., 2009; Sampson and Ho, 1997; Sampson, 2001). IgE cut-off levels for predicting lupin reactivity have not been established. FDA also found that only about one third of total patients in the applicant's sera study had evidence of IgE to Ara h 1 peanut protein, the relevant allergen in the diagnostic work-up for determining whether BLAD would pose a potential cross-reactive hazard for peanut-allergic individuals. Although BLAD was not shown to bind IgE in these subjects, the number of patients analyzed is too small to draw any meaningful statistical predictions of lack of allergenicity to BLAD for the general peanut-allergic population. (*Id*. at 6).

FDA again noted that "[r]ecruiting patients who had gone through and were observed to be reactive to peanut and/or lupin by the 'gold standard' food challenge would have helped to eliminate these uncertainties about the robustness of the allergic sera characterization." (*Id*.)

Finally, FDA expressed concern about the quality of the testing data, including an inadequate description of the methodology used and poor quality of the sera blot analyses, which further limit the ability to draw conclusions about the results of the sera testing. (*Id*.)

EPA gives great weight to FDA's expertise on the issue of allergenicity, given FDA's role in assessing food safety and their experience in evaluating foods for potential allergenicity concerns. As such, EPA has considered many of the concerns raised by FDA in its own analysis of the submitted data. After its initial conclusion that the lack of evidence of sera reactivity to BLAD provides an indication that BLAD may not be an allergen, EPA, taking into consideration FDA's concerns and the Codex Guideline warning that negative serum testing results may not be sufficient to disprove allergenicity, reexamined the adequacy of the submitted sera testing. (Ref. 6).

According to the Codex Guideline, "the availability of human sera from a sufficient number of individuals" and the "quality of the sera" are important to ensure the validity of the test results. For the present situation, the quality of the sera is the more significant issue for the BLAD test results. In order to evaluate the quality of the sera, EPA looks to the 2001 FAO/WHO Report, which cautions that patients should be carefully selected to ensure an adequate level of sensitivity to the protein. (Ref. 2 at 7). If patients have a low level of sensitization, then the usefulness of the sera to predict reactivity will be compromised. (*Id*.) In other words, the sera must be from patients whose allergenicity has been verified and who are sufficiently sensitive so that the sera will react to the allergen. If sera used is taken from patients who have not had their allergy verified or who may have low levels of allergic reaction (i.e., are insufficiently sensitive to the allergens), the sera may not react to the test substance, giving a negative result that cannot be extrapolated to the larger population of allergic or sensitized individuals. This result would undermine the reliability of the study results for disproving allergenicity, which can be especially problematic for substances derived from known allergens or that are similar or identical to known allergens.

Taking into consideration the need to ensure the quality of the sera and FDA's concerns about the quality of the sera used in the serum study, EPA has determined that the study characterization of recruited patients' clinical history of allergic reactions and lack of verification of allergenic reactivity raises uncertainties about the reliability of the study results to conclusively disprove BLAD's potential to pose an allergenic risk to lupin-sensitive and/or peanut-sensitive individuals. (Ref. 16). The quality of the sera being used as a test reagent is a critical issue in ensuring the reliability of the study results for predicting reactivity. (*Id*.) The selection of test subjects based on self-reported clinical symptoms without a food challenge-confirmed allergy, as well as the potential for false positives in skin prick tests, raise questions about the selection process, the adequacy of the IgE levels, and whether the study involved an adequate number of patients. (*Id*.) In other words, these facts introduce uncertainty about the quality of the sera and thus the reliability of the study results. Consequently, EPA does not consider this study to be scientifically reliable to overcome the presumption of allergenicity for BLAD, given the source of the protein and the bioinformatics analysis. (*Id*.)

B. Toxicological Points of Departure/Levels of Concern

The Agency did not identify any points of departure for BLAD. The toxicity database does not contain any indication of toxic effects as a basis for any toxicological points of departure or levels of concern. Moreover, there is no known threshold for allergenicity to BLAD. As a result, the Agency is not conducting a quantitative assessment of risk from potential BLAD exposure. Rather, the Agency's assessment of safety is based on the lack of exposure to BLAD because, as discussed in Unit V.C., the available residue data indicate that, when applied under current label rates and using good agricultural practices, there will be negligible to no detectable residues of BLAD on treated crops.

C. Exposure Assessment

1. *Dietary exposure from food and feed uses*. BLAD has been approved for use on several commodities; therefore, EPA evaluated the potential for BLAD residues on those crops in order to assess exposure.

CEV initially submitted residue data for grape, tomato, and strawberry. Field trials were conducted applying PROBLAD PLUS (a fungicide product containing BLAD at 20%) at the maximum product-labeled application rate (0.75 pounds of active ingredient per acre, five broadcast foliar applications per season, at 7-day intervals). Those studies showed that there were no quantifiable residues (where the LOQ is 0.02 ppm) on any treated grape, tomato, or strawberry commodities, and the majority of samples showed no residues above the level of detection (0.005 ppm). (Ref. 15). CEV later submitted additional field residue studies on cherry, cucumber, and apple that similarly demonstrated that application consistent with labeled rates resulted in residues at or below the level of detection of 0.005 ppm. (Ref. 17).

The Agency also requested that CEV conduct field trials using exaggerated application rates of 5X and 10X to determine the rate of BLAD residue degradation. Since the 10X concentration would be phytotoxic, CEV conducted field trials on tomatoes and strawberries using only the 5X application rate (3.75 pounds of active ingredient per acre). The decline curve for the treated commodities indicated a half-life of 2 days. Based on the measured residue levels in the study and using a first order degradation model, EPA was able to calculate a theoretical rate of degradation of 0.4215, which was then used to predict BLAD residues following treatment. (Ref. 15). Applying this degradation rate to residue levels observed in field residue data and taking into consideration the required 1-day interval between application and harvest of treated crops, the Agency expects that there will be no residues of BLAD above the level of

detection, if any remain at all, when commodities are treated in accordance with the label. (*Id*.) This rapid degradation rate is consistent with the expectation that BLAD, as a protein fragment, is susceptible to rapid degradation by environmental factors, such as microbial proteases. (Ref. 17).

Based on the available residue data, the Agency concludes that residues on grape, tomato, strawberry, apple, cherry, and cucumber will be below levels of detection and possibly non-existent when used in accordance with the label at the time of consumption. The Agency has also concluded that the available data is mutually supportive and is appropriate for supporting additional tolerances for certain crop groupings, hops, and almonds. (*Id*.)

Based on the available representative commodity data, the registrant requested use on and tolerances for the following crop groups: vegetable, fruiting, group 8-10; vegetable, cucurbit, group 9; fruit, pome, group 11-10; and fruit, stone, group 12-12. Although residue trials on all the representative commodities for those crop groups were not completed, the Agency has determined that trials on the remaining representative commodities are not necessary. The available residue data are mutually supportive and support a conclusion that any additional residue data for the other representative commodities would yield the same results. Given the similarity and consistency of the residue levels in these studies—in particular the consistency of results showing residues levels near or below the level of detection—the similarity in plant morphology between the representative commodity and the other commodities in the corresponding crop group, and the additional factors supporting the anticipated lack of exposure to residues of BLAD (i.e., rapid degradation rate and post-harvest interval), the Agency concludes that the available data are sufficient to support these crop groups. (*Id*.)

In addition, the Agency has concluded that no separate tolerances are needed for

processed commodities of the raw agricultural commodities contained in these crop groups. (*Id*.) The rapid degradation of BLAD by microbes on treated crops combined with the methods for processing these commodities (e.g., washing and pasteurizing) will reduce the already low levels of residues on the treated commodities. The tolerances being established are sufficient to cover residues in those processed commodities.

Moreover, although no residue field trials were submitted to support the hops, dried cones tolerance, the Agency has assessed the potential for exposure to BLAD residues on hops by examining the short environmental persistence of BLAD and the additional processing steps to which hops is subject prior to consumption. Following application of BLAD to hops, at rates that are the same as for other labeled crops, initial residues of BLAD are expected to rapidly degrade during the drying phase. The long drying time would also allow a longer time for microbial degradation of the protein. Furthermore, processing of hops, which is used as a flavoring and preservative in fermented beverages, is expected to further mitigate exposure prior to consumption. All of these factors suggest an elimination of potential residues on hops by the time of consumption. (*Id*.)

Because the application rates and methods are the same for grape and almond, the residue data can be translated to almond hulls, and the Agency has determined that the residues on almond hulls will be similar to residues found on strawberries, grapes, and tomatoes. (Ref. 18). The general practice for harvesting almonds, which typically involves 7-10 days of drying before processing, is likely to further reduce residues on the almond hulls. Also, because BLAD is not applied directly to the almonds, the Agency expects residues on the almond nutmeat itself to be even lower.

Because almond hulls are an animal feed item, section 180.6 of EPA's regulations

requires that EPA consider whether residues of BLAD present on animal feed items will result in residues of BLAD in meat, milk, eggs, or poultry commodities consumed by humans. 40 CFR 180.6(a). If there is no reasonable expectation of residues in the livestock commodities, the Agency can establish a tolerance on the raw agricultural commodity (in this case, the almond). 40 CFR 180.6(b). Based on the available information, EPA has concluded that the likely residues on almond hulls will be at or below levels of detection. Even if there are any residues remaining on almond hulls that are ingested by animals, EPA has concluded that there is not likely to be any residues in the livestock commodities. (Ref. 18). Due to its molecular size, BLAD is not expected to pass through biological membranes. Moreover, it is expected to be rapidly digested instead of accumulating in animal tissues. (*Id*.) As a result, there is no reasonable expectation of residues in livestock commodities and thus no need for associated livestock commodity tolerances.

2. *Dietary exposure from drinking water*. The Agency expects residues of BLAD in drinking water to be negligible. Because BLAD is applied foliarly, there is a chance that it may get into drinking water, but there is likely to be very little in the environment from applications. Moreover, what little residue may be present would likely be subject to potential photolysis and microbial degradation due to its nature as a protein.

3. *From non-dietary exposure*. The term "residential exposure" is used in this document to refer to non-occupational, non-dietary exposure (e.g., for lawn and garden pest control, indoor pest control, termiticides, and flea and tick control on pets). BLAD is not registered for any specific use patterns that would result in residential exposure.

4. *Cumulative effects from substances with a common mechanism of toxicity*. Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or

revoke a tolerance, the Agency consider "available information concerning the cumulative effects of [a particular pesticide's] … residues and other substances that have a common mechanism of toxicity."

EPA has not found BLAD to share a common mechanism of toxicity with any other substances, and BLAD does not appear to degrade into any toxic metabolite or other substance of concern. For the purposes of this tolerance action, therefore, EPA has assumed that BLAD does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at *https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides*.

D. Safety Factor for Infants and Children

FFDCA section 408(b)(2)(C) provides that, in considering the establishment of a tolerance or tolerance exemption for a pesticide chemical residue, EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure, unless EPA determines that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the Food Quality Protection Act Safety Factor. In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data are available to support the choice of a different safety factor.

Because the Agency has not identified any threshold effects for BLAD, this additional safety factor is not applicable for assessing risk to infants and children.

E. Aggregate Risks and Determination of Safety

EPA has evaluated the available toxicity, allergenicity, and exposure data and considered its validity, completeness, and reliability, as well as the relationship of the results of the studies to human risk. Taking into consideration all available information on BLAD, EPA cannot conclude that unlimited exposures to BLAD on all food crops would not pose a risk of allergenicity to lupin-sensitive or peanut-sensitive individuals. The data submitted on the potential allergenicity does not overcome the burden for demonstrating that BLAD is not an allergen, given that BLAD is derived from a known allergenic source and the bioinformatics analysis demonstrates sequence similarity with other major allergens. Based on this information, the Agency can no longer support a safety determination for an unlimited exemption from the requirement of a tolerance for residues of BLAD on all food commodities. As a result, EPA is proposing to revoke the current tolerance exemption for BLAD found in 40 CFR 180.1319.

Although EPA can no longer support the existing tolerance exemption for BLAD, which, on its face, places no limits on the levels of BLAD residues on any food commodities, EPA has determined, based on residue data supporting a conclusion of negligible to no exposure to BLAD residues on certain crops, that certain limited tolerances would be safe. That is, there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of BLAD when it is applied as a fungicide in accordance with label directions and good agricultural practices on the following commodities: almond; almond, hulls; fruit, pome, group 11-10; fruit, stone, group 12-12; grape; hops, dried cones; strawberry; vegetable, cucurbit, group 9; and vegetable, fruiting, group 8-10. Such exposure includes all anticipated dietary exposures and all other exposures for which there is reliable information.

Upon consideration of information regarding the likely levels of exposure to BLAD from approved use patterns, EPA concludes that the approved uses of BLAD are unlikely to result in residues above the level of detection when shipped in interstate commerce. Further, based on expected degradation rates, the Agency expects residue levels at the time of consumption to be even lower, likely non-existent. The lack of exposure to detectable residues of BLAD, if there are any residues at all, is the basis for the Agency's safety finding for these tolerances.

While the Agency, as a general matter, expects users to follow label directions on pesticide products and that residue data indicate that application in accordance with the label results primarily in undetectable residues or levels at or below levels of detection, EPA is proposing to establish tolerances at the lowest level for measuring quantifiable residues of BLAD (0.02 ppm). Given the potential severity of allergic reactions, the Agency believes that setting numerical tolerances, rather than leaving in effect an unlimited exemption, is the appropriate regulatory mechanism for monitoring residues and facilitates the removal of adulterated commodities from the food supply if residues are found above tolerance levels on any of these commodities. The expectation of negligible to no residues under proper use conditions, subject to the mechanisms of enforcement under the FFDCA and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), provide assurance that consumers will not be exposed to residues of BLAD that may cause harm. Therefore, EPA is proposing to revoke the current exemption and establish tolerances for residues of BLAD in or on the following commodities at 0.02 ppm: almond; almond, hulls; fruit, pome, group 11-10; fruit, stone, group 12-12; grape; hops, dried cones; strawberry; vegetable, cucurbit, group 9; and vegetable, fruiting, group 8-10.

VI. Other Considerations

A. Analytical Enforcement Methodology

Adequate enforcement methodology (Enzyme-Linked Immunosorbent Assay (ELISA: EASI Method No: RA029 and RA031)) is available to enforce the tolerance expression.

The method may be requested from: Chief, Analytical Chemistry Branch, Environmental Science Center, 701 Mapes Rd., Ft. Meade, MD 20755-5350; telephone number: (410) 305-2905; email address: *residuemethods@epa.gov*.

B. International Residue Limits

In making its tolerance decisions, EPA seeks to harmonize U.S. tolerances with international standards whenever possible, consistent with U.S. food safety standards and agricultural practices. EPA considers the international maximum residue limits (MRLs) established by the Codex Alimentarius Commission (Codex), as required by FFDCA section 408(b)(4). The Codex Alimentarius is a joint FAO/WHO food standards program, and it is recognized as an international food safety standards-setting organization in trade agreements to which the United States is a party. EPA may establish a tolerance that is different from a Codex MRL; however, FFDCA section 408(b)(4) requires that EPA explain the reasons for departing from the Codex level.

The Codex has not established an MRL for BLAD.

C. Trade and Economic Considerations

The Agency received comments on its May 29, 2015, proposal about the potential impact of the proposal on trade and farmers. The commenters alleged that the proposal failed to address possible impacts on international trade, including the potential to cause other countries to require or amend MRLs, to develop enforcement procedures consistent with international regulatory data requirements, and to impose new and more onerous data requirements. The commenters also

expressed concern about the lack of harmonization with Canada, which has decided not to regulate residues of BLAD, and pointed to the potential for disruption in trade between the United States and Canada, or at least confusion at the border for enforcing the different standards, as a result. In addition, many commenters expressed concern that the proposal revoking the exemption would have an adverse impact on farmers who relied on BLAD as an effective fungicide.

Under the FFDCA, tolerances and exemptions from the requirement of a tolerance may be established when EPA determines that they are safe. 21 U.S.C. 346a(b)(2)(A)(i), *(c)(2)(A)(i)*. The FFDCA also requires that EPA revoke tolerances or exemptions when it determines they are not safe. *Id*. This safety assessment is a risk-only assessment, not a risk-benefit standard. In essence, the statute directs that whether EPA can leave in effect or establish a tolerance or exemption is based solely on the Agency's assessment of the risk to human health and not a balancing of other non-safety factors (e.g., impact on trade or impact on farmers) with the risk. The FFDCA directs EPA to consider several factors relevant to the safety of the pesticide residue in food (aggregated with other sources of exposure to the pesticide residue), placing particular emphasis on human dietary risk. *See, e.g., 21 U.S.C. 346a(b)(2)(B)* (addressing an exception to the safety standard for pesticide residues as to which EPA "is not able to identify a level of exposure to the residue at which the residue will not cause or contribute to a known or anticipated harm to human health"); *21 U.S.C. 346a(b)(2)(C)* (requiring special safety findings as to "infants and children" regarding their "disproportionately high consumption of foods" and their "special susceptibility * * * to pesticide chemical residues"); *21 U.S.C. 346a(b)(2)(D)(iii)* (requiring consideration of the relationship between toxic effects found in pesticide studies and human risk); *21 U.S.C. 346a(b)(2)(D)(iv), (vi), and (vii)* (requiring consideration of available

information on "dietary consumption patterns of consumers," "aggregate exposure levels of consumers," and the "variability of the sensitivities of major identifiable subgroups of consumers"); *21 U.S.C. 346a(b)(2)(D)(vi)* (requiring consideration of "non-occupational" sources of exposure); *21 U.S.C. 346a(b)(2)(D)(viii)* (requiring consideration of information bearing on whether a pesticide "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects"); *21 U.S.C. 346a(l)(2) and (3)* (requiring revocation or suspension of tolerances where associated FIFRA registration is canceled or suspended "due in whole or in part to dietary risks to humans posed by residues of that pesticide chemical on that food").

The only mention of a factor relevant to trade is found in FFDCA section 408(b)(4), which, as noted in Unit VI.B., requires EPA to determine whether an MRL has been established by Codex when establishing a tolerance and to explain its reasons for departing from that level, if applicable. 21 U.S.C. 346a(b)(4). Here, as noted above, Codex has not established any MRLs for BLAD; therefore, there is nothing to harmonize and no discrepancies to explain. As a matter of policy and where the Agency can support the safety finding, EPA seeks to harmonize U.S. tolerances whenever possible with Codex MRLs and the MRLs of other trading partners, including Canada, consistent with U.S. food safety standards and agricultural practices. For BLAD, based on the available information, EPA can no longer maintain the safety finding to support the unlimited tolerance exemption for BLAD residues on all commodities. Harmonization with Canada's regulatory approach is not a legal basis for retaining the exemption under the FFDCA when EPA concludes that the exemption is not safe.

Notwithstanding the substantive restrictions of the FFDCA, EPA recognizes the obligations of the United States to comply with the procedural obligations under the World Trade

Organization's Sanitary and Phytosanitary Measures Agreement (SPS Agreement). Because the proposal is a regulation subject to the requirements of the SPS Agreement, EPA intends to comply with the provisions of that Agreement, including those related to notification and implementation, including allowing for a 6-month delay in the exemption revocation to provide exporting countries a period of time to adjust to the U.S. new tolerances. In any event, the revocation in this proposal is not discriminatory and is designed to ensure that both domestically produced and imported foods meet the food safety standard established by the FFDCA.

VII. Conclusion

EPA proposes to revoke the existing tolerance exemption for residues of BLAD in or on all food commodities as established in the **Federal Register** of March 22, 2013 (78 FR 17600) (FRL-9380-6) under section 408 of the FFDCA. Based on the available information, EPA can no longer support the safety finding necessary to maintain the exemption. Notwithstanding the Agency's conclusions concerning the unlimited exemption, the Agency has determined that the available information supports a safety finding for the tolerances for residues of BLAD in or on almond; almond, hulls; fruit, pome, group 11-10; fruit, stone, group 12-12; grape; hops, dried cones; strawberry; vegetable, cucurbit, group 9; and vegetable, fruiting, group 8-10 at 0.02 ppm. Therefore, EPA is proposing to establish tolerances for residues of BLAD on those commodities.

VIII. References

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

INFORMATION CONTACT.

1. U.S. Food and Drug Administration (FDA). Letter from Michael A. Adams, Ph.D., Deputy Director of Office of Food Additive Safety (FAS), Center for Food Safety and Applied Nutrition (CFSAN) to Menyon Adams, Biopesticides and Pollution Prevention Division (BPPD), Office of Pesticide Programs (OPP), re: Docket Number EPA-HQ-OPP-2011-1026. May 21, 2013.

2. Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO). Evaluation of Allergenicity of Genetically Modified Foods: Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology. January 2001.

3. WHO/FAO. Codex Alimentarius: Foods Derived from Modern Biotechnology. 2009.

4. U.S. Environmental Protection Agency (EPA). Memorandum from Miachel Rexrode, Ph.D., Senior Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD). Request for New Product Registration for β-Conglutin Section 3 with Tolerance. May 24, 2012.

5. European Food Safety Authority (EFSA). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a Request from the Commission Related to the Evaluation of Lupin for Labelling Purposes. (Request No. EFSA-Q-2005-086). The EFSA Journal (2005) 302, 1-11. December 6, 2005.

6. U.S. EPA. Memorandum from John L. Kough, Ph.D., Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD). Review of Allergenicity Decisions on BLAD. December 9, 2015.

7. U.S. EPA. Memorandum from Robert McNally, Director, BPPD, OPP to Dennis M. Keefe, Ph.D., Director, CFSAN, FAS. Request for Specific Input from FDA to Assist EPA in

Addressing Comments Received in Response to EPA's Proposal Regarding Banda de *Lupinus alba* doce (BLAD). December 7, 2015.

8. U.S. Department of Health and Human Services (HHS). Memorandum from Stefano Luccioli, MD, Medical Officer, FAS, CFSAN to Dennis Keefe, Ph.D., Director, FAS, CFSAN. Response to EPA Questions in Memorandum Dated December 7, 2015, Regarding BLAD Biopesticide. December 17, 2015.

9. EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the Evaluation of Allergenic Foods and Food Ingredients for Labelling Purposes. EFSA Journal 2014;12(11):3894, 286 pp. doi:10.2903/j.efsa.2014.3894. November 26, 2014.

10. Commission Directive 2006/142/EC (December 22, 2006), amending Annex IIIa of European Directive 2000/13/EC (March 20, 2000).

11. U.S. FDA. Allergies to a Legume Called Lupin: What You Need to Know. *https://www.fda.gov/consumers/consumer-updates/allergies-legume-called-lupin-what-you-need-know* (last checked May 31, 2019).

12. U.S. FDA. Frequently Asked Questions on Lupin and Allergenicity. *https://www.fda.gov/food/food-additives-petitions/lupin-and-allergenicity-frequently-asked-questions* (last checked May 30, 2019).

13. World Health Organization/International Union of Immunological Sciences. Allergen Nomenclature. Allergen details for Lup an 1. *http://www.allergen.org/viewallergen.php?aid=421* (last checked May 31, 2019).

14. U.S. EPA. Memorandum from Miachel Rexrode, Ph.D., Senior Biologist (BPPD) to Linda Hollis, Chief, Biochemical Pesticides Branch (BPB), BPPD. BLAD Data Requirements.

May 15, 2013.

15. U.S. EPA. Memorandum from Miachel Rexrode, Ph.D., Senior Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD). Evaluation of New Serum Testing and Field Residue Decline Study for BLAD. June 6, 2014. As corrected by the following document: U.S. EPA. Memorandum from Miachel Rexrode, Ph.D., Senior Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD). December 28, 2016.

16. U.S. EPA. Memorandum from John L. Kough, Ph.D., Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD) and Linda Hollis, Branch Chief, BPB, BPPD. Review of FDA Interactions on the Allergenicity Assessment of Banda de *Lupinus alba* (BLAD) from CEV. August 23, 2016.

17. U.S. EPA. Memorandum from John L. Kough, Ph.D., Biologist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD). Review of Crop Groupings for PROBLAD PLUS. June 26, 2019.

18. U.S. EPA. Memorandum from Judy Facey, Ph.D., Associate Branch Chief (Acting), BPB, BPPD and John L. Kough, Ph.D., Senior Scientist (BPPD) to Menyon Adams, Regulatory Action Leader (BPPD) and Linda Hollis, Branch Chief, BPB, BPPD. ChemSAC Conclusion on: Potential BLAD Residues in Meat or Milk from Almond Hull Feed Consumption Resulting from Almond Treatment. January 24, 2017.

19. U.S. EPA. Memorandum from Denise Keehner, Division Director, Biological and Economic Analysis Division, OPP to Public Docket concerning Tolerance Revocation Rulemaking, Proposed or Final. RFA/SBREFA Certification for Import Tolerance Revocation. May 25, 2001.

IX. Statutory and Executive Order Reviews

Although this proposed action would revoke an existing exemption from the requirement of a tolerance, it also would establish new tolerances that would cover pesticide chemical residues resulting from existing registered uses under FFDCA section 408(e). The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Orders 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993), and 13563, entitled *Improving Regulation and Regulatory Review* (76 FR 3821, January 21, 2011). As a result, this action 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). 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). Nor is this action considered a regulatory action subject to review under Executive Order 13771, entitled *Reducing Regulations and Controlling Regulatory Costs* (82 FR 9339, February 3, 2017).

This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (44 U.S.C. 3501 *et seq*.); 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); and does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (15 U.S.C. 272 note).

This action directly regulates growers, food processors, food handlers, and food retailers, but it does not regulate State or tribal governments. Nor does this action alter the relationships or distribution of power and responsibilities established in the preemption provisions of FFDCA

section 408(n)(4). Therefore, the Agency has determined that Executive Orders 13132, entitled *Federalism* (64 FR 43255, August 10, 1999), and 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 9, 2000), do not apply to this action. In addition, this action does not impose any enforceable duty, contain any unfunded mandate, or otherwise significantly or uniquely affect small governments as described in the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq*.).

Pursuant to the Regulatory Flexibility Act (5 U.S.C. 601 *et seq*.), the Agency previously assessed whether establishment of tolerances, exemptions from tolerances, raising of tolerance levels, expansion of exemptions, or revocations might significantly impact a substantial number of small entities and concluded that, as a general matter, these actions do not impose a significant economic impact on a substantial number of small entities. These analyses for tolerance establishments and modifications and for tolerance revocations were published in the **Federal Register** of May 4, 1981 (46 FR 24950) (FRL-1809-5) and December 17, 1997 (62 FR 66020) (FRL-5753-1), respectively, and were provided to the Chief Counsel for Advocacy of the Small Business Administration. Taking into account this analysis, and available information concerning the pesticide listed in this proposed rule, the Agency hereby certifies that this proposed rule will not have a significant negative economic impact on a substantial number of small entities. In a memorandum dated May 25, 2001, EPA determined that eight conditions must all be satisfied in order for an import tolerance or tolerance exemption revocation to adversely affect a significant number of small entity importers, and that there is a negligible joint probability of all eight conditions holding simultaneously with respect to any particular revocation. (Ref. 19). Furthermore, for BLAD, the Agency knows of no extraordinary circumstances that exist as to the present proposed rule that would change EPA's previous

analysis. Any comments about the Agency's determination should be submitted to EPA along with comments on the proposed rule and will be addressed prior to issuing a final rule.

List of Subjects in 40 CFR Part 180

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

Dated: January 21, 2020.

Richard Keigwin,

Director, Office of Pesticide Programs.

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

PART 180--[AMENDED]

1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

2. Add § 180.707 to subpart C to read as follows:

§ 180.707 Banda de *Lupinus albus* doce (BLAD); tolerances for residues.

(a) *General*. Tolerances are established for residues of the fungicide banda de *Lupinus albus* doce (BLAD), including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only BLAD in or on the following commodities.

Commodity	Parts per million
Almond	0.02
Almond, hulls	0.02
Fruit, pome, group 11-10	0.02
Fruit, stone, group 12-12	0.02
Grape	0.02
Hops, dried cones	0.02
Strawberry	0.02
Vegetable, cucurbit, group 9	0.02
Vegetable, fruiting, group 8-10	0.02

(b) *Section 18 emergency exemptions*. [Reserved]

(c) *Tolerances with regional registrations*. [Reserved]

(d) *Indirect or inadvertent residues.* [Reserved]

3. Revise § 180.1319 in subpart D to read as follows:

§ 180.1319 Banda de *Lupinus albus* doce (BLAD); exemption from the requirement of a tolerance.

An exemption from the requirement of a tolerance is established for the residues of Banda de *Lupinus albus* doce (BLAD), a naturally occurring polypeptide from the catabolism of

a seed storage protein (β-conglutin) of sweet lupines (*Lupinus albus*), in or on all food commodities when applied as a fungicide and used in accordance with label directions and good agricultural practices. This exemption expires on [*insert date 6 months after date of publication of final rule in the* **Federal Register**].

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