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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2010-0051; FRL-9381-1]

Amitraz; Pesticide Tolerances

AGENCY: Environmental Protection Agency (EPA).
ACTION: Final rule.
SUMMARY: This regulation establishes tolerances for residues of amitraz in or on honey and honeycomb. Arysta Lifescience America, Inc. requested the tolerance for honey under the Federal Food, Drug, and Cosmetic Act (FFDCA).

DATES: This regulation is effective **[***insert date of publication in the* **Federal Register]**. Objections and requests for hearings must be received on or before **[***insert date 60 days after date of publication in the* **Federal Register]**, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2010-0051 is available at *http://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), EPA West Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Stacey Groce, Registration Divison, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 305-2505; e-mail address: *groce.stacey@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. *How Can I Get Electronic Access to Other Related Information?*

You may access a frequently updated electronic version of EPA's tolerance regulations at 40 CFR part 180 through the Government Printing Office's e-CFR site at *http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl*.

C. *How Can I File an Objection or Hearing Request?*

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the

instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2010-0051 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before **[***insert date 60 days after date of publication in the* **Federal Register]**. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2010-0051 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/contacts.htm*.

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

II. Summary of Petitioned-For Tolerance

In the **Federal Register** of March 24, 2010 (75 FR 14154) (FRL-8815-6), EPA issued a document pursuant to FFDCA section 408(d)(3), 21 U.S.C. 346a(d)(3), announcing the filing of a pesticide petition (PP 9F7673) by Veto-Pharma SA, c/o Arysta LifeScience America, 1450 Broadway, 7th Floor, New York, NY 10018. The petition requested that 40 CFR 180.287 be amended by establishing tolerances for residues of the insecticide, amitraz, (N'-[2,4-dimethylphenyl]-N-[[(2,4-dimethylphenyl)imino]methyl]]-N-methylmethanimidamide) in or on honey at 1 part per million (ppm). That document referenced a summary of the petition prepared by Veto-Pharma, SA c/o Arysta, the registrant, which is available to the public in the docket, *http://www.regulations.gov*. There were no comments received in response to the notice of filing.

Based upon review of data supporting the petition, EPA is establishing a lower tolerance for honey than was requested and is establishing a tolerance for honeycomb. The reasons for these changes are explained in detail in Unit IV.C.

III. Aggregate Risk Assessment and Determination of Safety

Section 408(b)(2)(A)(i) of FFDCA 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." Section 408(b)(2)(A)(ii) of FFDCA defines "safe" to mean that "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." This includes exposure through drinking water and

in residential settings, but does not include occupational exposure. Section 408(b)(2)(C) of FFDCA 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...."

Consistent with FFDCA section 408(b)(2)(D), and the factors specified in FFDCA section 408(b)(2)(D)**,** EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for amitraz including exposure resulting from the tolerances established by this action. EPA's assessment of exposures and risks associated with amitraz follows.

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.

Acute toxicity studies in various laboratory animals indicate that amitraz is moderately toxic via the dermal route, and it is slightly toxic via the oral and not acutely toxic via inhalation routes of exposure. Further, it is not a skin or eye irritant, nor is it a skin sensitizer.

Multiple species display evidence of neurotoxicity following exposure to amitraz. Clinical signs of neurotoxicity were seen across species, sexes, and routes of

administration. Based on available human and animal studies, human subjects were shown to be more sensitive than any other species tested, followed by the dog. In both the oral subchronic and chronic studies in dogs, signs of central nervous system depression were observed along with a decrease in pulse rate and hypothermia noted in the subchronic study. In both the oral subchronic and chronic studies and in the 21-day inhalation study in the rat, irritability, nervousness and/or excitability were observed. In the rabbit developmental toxicity study, clinical signs that were considered to be related to treatment included languor and polypnea. Sedation was also observed in rabbits in the repeated dose dermal study. In the single dose human metabolism study, neurotoxic effects such as dry mouth, drowsiness, decreased temperature, and bradycardia were seen within 90 to 160 minutes after ingestion and persisted for up to 12 hours at the lowest dose tested (0.25 mg/kg/day).

No developmental toxicity was seen at the highest dose tested in two pre-natal developmental toxicity studies in rats. Two independent developmental toxicity studies were available in rabbits. Although technical deficiencies were encountered in the conduct of these studies, no developmental effects were seen either at the highest dose tested (in one study) or in the presence of maternal toxicity (second study). When taken together, these studies show that (1) amitraz does not cause developmental toxicity in this species and (2) rabbits are not more sensitive than rats since the doses tested in the rabbits were higher than the doses tested in the rat developmental study where no developmental toxicity was seen at any dose level. The database contains a 1-generation and a 3-generation reproduction study in rats. In the 1-generation study, no reproductive toxicity was seen at the highest dose tested and offspring toxicity was seen in the presence of

parental/systemic toxicity. In the 3-generation reproduction study, no reproductive toxicity was seen at the highest dose tested, however, offspring toxicity was seen at a lower dose than the dose that caused parental/systemic toxicity.

The CNS effects of amitraz do not appear to be cumulative, i.e., do not accumulate with increased duration. In the 90-day repeat dose dog study, the CNS effects appear early on (within 3 hours of dosing), rapidly end, and recur daily after dosing throughout the study. In the chronic (2-year) dog study, the CNS effects are seen following a single dose on the first 2 days of the study, with transient hypothermia detected in only one female throughout the rest of the study, indicative of some potential adaptation occurring at lower doses over longer periods of testing. The NOAEL and LOAEL for the 90-day and chronic dog studies are the same, also indicating that the CNS effects are not cumulative, but are a response to each daily dose that is likely reversible if exposure were to stop. Additionally, the single dose (acute) studies across several species show an onset of CNS effects within a few hours and recovery within a few hours to several days. The human metabolism study showed neurotoxic effects shortly after dosing, which disappeared within 12 hours. Although the metabolism study was limited to two subjects, both human subjects exposed experienced clear CNS effects that were consistent with the animal data. Because of the reversibility of the CNS effects, exposures of all durations can be regarded as a series of repeating one-day (acute) exposures.

For other effects, such as body weight changes and the tumors in the mouse study, those effects are likely to be cumulative. However, those effects occur at higher dose levels than the CNS depression. The human endpoint (0.125 mg/kg/day) will be

protective of other longer term systemic effects as it is a lower dose level than the dose levels where these other systemic effects such as body weight change occur.

Although a mouse carcinogenicity study showed that amitraz was associated with common tumors (liver and lung) in the mouse, EPA has determined that quantification of risk using a non-linear approach (*i.e.,* RfD) for amitraz will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to amitraz and its metabolites. That conclusion is based on the following considerations: (1) No carcinogenic response was seen in an acceptable rat cancer study; (2) the tumors found in the mouse are commonly seen in the mouse and were only found at a dose that appears to have been excessive given the other adverse effects seen in the animals; (3) amitraz is not mutagenic; and (4) although there is limited positive mutagenicity data and equivocal evidence of cancer for a minor amitraz metabolite, that equivocal cancer evidence was present only at high doses and was not consistent with the tumors seen in the amitraz study.

More detailed information on the studies received and the nature of the adverse effects caused by amitraz as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies can be found at http://*www.regulations.gov* in the document entitled, "Amitraz: Aggregate Human Health Risk Assessment for Section 3 New Use in Beehives," dated January 8, 2013, by going to *http://www.regulations.gov*. The referenced document is available in the docket established by this action, which is described under **ADDRESSES**. Locate and click on the hyperlink for docket ID number EPA-HQ-OPP-2010-0051. Double-click on the document to view the referenced information on pages 15-19 of 48.

B. *Toxicological Points of Departure/Levels of Concern*

Once a pesticide's toxicological profile is determined, EPA identifies toxicological points of departure (POD) and levels of concern to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk assessment. PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which no adverse effects are observed (the NOAEL) and the lowest dose at which adverse effects of concern are identified (the LOAEL). Uncertainty/safety factors are used in conjunction with the POD to calculate a safe exposure level - generally referred to as a population-adjusted dose (PAD) or a reference dose (RfD) - and a safe margin of exposure (MOE). For non-threshold risks, the Agency assumes that any amount of exposure will lead to some degree of risk. Thus, the Agency estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see *http://www.epa.gov/pesticides/factsheets/riskassess.htm*.

A summary of the toxicological endpoints for amitraz used for human risk assessment is shown in the table of this unit.

Table -- Summary of Toxicological Doses and Endpoints for Amitraz for Use in Human Health Risk Assessment

Exposure/Scenario	Point of Departure and Uncertainty/Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects

Acute dietary (General population including infants and children)	NOAEL = 0.125 mg/kg/day UF_H = 10x FQPA SF = UF_{DB} = 10x	Acute RfD = 0.0125 mg/kg/day aPAD = 0.00125 mg/kg/day	A double-blind randomized crossover study in human subjects LOAEL = 0.25 mg/kg/day based on dry mouth, drowsiness, decreased temperature, decreased blood pressure and decreased heart rate.
Incidental oral short- and intermediate term	NOAEL= 0.125 mg/kg/day UF_H = 10x FQPA SF = UF_{DB} = 10x	Residential LOC for MOE = 100	A double-blind randomized crossover study in human subjects LOAEL = 0.25 mg/kg/day based on dry mouth, drowsiness, decreased temperature, decreased blood pressure and decreased heart rate.
Dermal (All durations)	Oral NOAEL = 0.125 mg/kg/day Dermal Absorption Rate = 1.6% UF_H = 10x FQPA SF = UF_{DB} = 10x	Residential LOC for MOE = 100	A double-blind randomized crossover study in human subjects LOAEL = 0.25 mg/kg/day based on dry mouth, drowsiness, decreased temperature, decreased blood pressure and decreased heart rate.
Inhalation (All durations)	Oral NOAEL = 0.125 mg/kg/day UF_H = 10x FQPA SF = UF_{DB} = 10x	Residential LOC for MOE = 100	A double-blind randomized crossover study in human subjects LOAEL = 0.25 mg/kg/day based on dry mouth, drowsiness, decreased temperature, decreased blood pressure and decreased heart rate.
Cancer (Oral, dermal, inhalation)	EPA has determined that quantification of risk using a non-linear approach (*i.e.,* RfD) will adequately account for all chronic toxicity, including carcinogenicity. Because of the reversibility of the CNS effects, exposures of all durations can be regarded as a series of repeating one-day (acute) exposures and there is no increase in hazard with increasing dosing duration. Therefore, the acute dietary endpoint is protective of the endpoints from repeat dosing studies, including cancer dietary exposures.		

FQPA SF = Food Quality Protection Act Safety Factor. LOAEL = lowest-observed-adverse-effect-level. LOC = level of concern. mg/kg/day = milligram/kilogram/day. MOE = margin of exposure. NOAEL = no-observed-adverse-effect-level. PAD = population adjusted dose (a = acute). RfD = reference dose. UF_{DB} = to account for the absence of data or other data deficiency. UF_H = potential variation in sensitivity among members of the human population (intraspecies).

C. *Exposure Assessment*

1. *Dietary exposure from food and feed uses*. In evaluating dietary exposure to amitraz, EPA considered exposure under the petitioned-for tolerances as well as all existing amitraz tolerances in 40 CFR 180.287. EPA assessed dietary exposures from amitraz in food as follows:

i. *Acute exposure*. Quantitative acute dietary exposure and risk assessments are performed for a food-use pesticide, if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1-day or single exposure.

Such effects were identified for amitraz. In estimating acute dietary exposure, EPA used food consumption information from the United States Department of Agriculture (USDA) 1994-1996 and 1998 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII). As to residue levels in food, EPA conducted a partially refined acute dietary analysis using the Dietary Exposure Evaluation Model DEEM-FCID™, Version 2.03 and assumed exposure through honey, imported cottonseed oil, meat and milk from dermal treatments of livestock. The residue values used for livestock products, except for milk, are based upon tolerance level residues. Milk residues were assessed using the high-end result from the original cattle dosing study. Percents of livestock treated were used. Residues in cottonseed oil were estimated using the tolerance level and percent crop imported. For honey, residue values from field trial data and 100% crop treated were used.

ii. *Chronic exposure*. Based on data summarized in Unit lll.A., there is no increase in hazard from repeated exposures to amitraz; as such the acute dietary exposure assessment is protective of any chronic dietary exposures to amitraz because there is no

increase in hazard with increasing dosing duration. Accordingly, a dietary exposure assessment for the purpose of assessing chronic dietary risk was not conducted.

iii. *Cancer*. EPA determines whether quantitative cancer exposure and risk assessments are appropriate for a food-use pesticide based on the weight of the evidence from cancer studies and other relevant data. If quantitative cancer risk assessment is appropriate, cancer risk may be quantified using a linear or nonlinear approach. If sufficient information on the carcinogenic mode of action is available, a threshold or nonlinear approach is used and a cancer RfD is calculated based on an earlier noncancer key event. If carcinogenic mode of action data is not available, or if the mode of action data determines a mutagenic mode of action, a default linear cancer slope factor approach is utilized. Based on the data summarized in Unit III.A., the Agency has determined that quantification of risk using a nonlinear approach (i.e., RfD) would adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to amitraz. Therefore, the acute dietary assessment is protective of any cancer effects resulting from amitraz residues in food.

iv. *Anticipated residue and percent crop treated (PCT) information*. Section 408(b)(2)(E) of FFDCA authorizes EPA to use available data and information on the anticipated residue levels of pesticide residues in food and the actual levels of pesticide residues that have been measured in food. If EPA relies on such information, EPA must require pursuant to FFDCA section 408(f)(1) that data be provided 5 years after the tolerance is established, modified, or left in effect, demonstrating that the levels in food are not above the levels anticipated. For the present action, EPA will issue such data call-ins as are required by FFDCA section 408(b)(2)(E) and authorized under FFDCA section

408(f)(1). Data will be required to be submitted no later than 5 years from the date of issuance of these tolerances.

Section 408(b)(2)(F) of FFDCA states that the Agency may use data on the actual percent of food treated for assessing chronic dietary risk only if:

• Condition a: The data used are reliable and provide a valid basis to show what percentage of the food derived from such crop is likely to contain the pesticide residue.

• Condition b: The exposure estimate does not underestimate exposure for any significant subpopulation group.

• Condition c: Data are available on pesticide use and food consumption in a particular area, the exposure estimate does not understate exposure for the population in such area.

In addition, the Agency must provide for periodic evaluation of any estimates used. To provide for the periodic evaluation of the estimate of PCT as required by FFDCA section 408(b)(2)(F), EPA may require registrants to submit data on PCT.

The Agency estimated the PCT for existing uses as follows:

Cotton seed oil, 2%; beef meat, 0.3%; beef meat dried, 0.3%; beef meat byproducts, 0.3%; beef fat, 0.3%; beef kidney, 0.3%; beef liver, 0.3%; pork meat, 1.2%, pork skin, 1.2%; pork meat byproducts, 1.2%; pork fat, 1.2%; pork kidney, 1.2%; pork liver, 1.2%; milk fat, 0.3%; milk non-fat solids, 0.3%; milk water, 0.3%; milk sugar, 0.3%.

In most cases, EPA uses available data from United States Department of Agriculture/National Agricultural Statistics Service (USDA/NASS), proprietary market surveys, and the National Pesticide Use Database for the chemical/crop combination for the most recent 6-7 years. EPA uses an average PCT for chronic dietary risk analysis.

The average PCT figure for each existing use is derived by combining available public and private market survey data for that use, averaging across all observations, and rounding to the nearest 5%, except for those situations in which the average PCT is less than one. In those cases, 1% is used as the average PCT and 2.5% is used as the maximum PCT. EPA uses a maximum PCT for acute dietary risk analysis. The maximum PCT figure is the highest observed maximum value reported within the recent 6 years of available public and private market survey data for the existing use and rounded up to the nearest multiple of 5%.

For this request, the EPA relied on available data in USDA NASS for cattle and swine to determine the percent of animal heads treated with amitraz. NASS does not report the total number of dairy cattle treated with a particular chemical because the applications vary significantly based on product formulation, method of application, and pest stress at particular locations. Rather, they report chemical usage on a rate per head per application and rate per head per year basis. To determine the number of cattle treated, EPA divided the total pounds of amitraz applied by the total rate per head per year, which NASS defines as the *average* number of pounds applied counting multiple applications. It was assumed that the average rate captures the variation in number of cows treated.

The Agency believes that the three conditions discussed in Unit III.C.1.iv. have been met. With respect to Condition a, PCT estimates are derived from Federal and private market survey data, which are reliable and have a valid basis. The Agency is reasonably certain that the percentage of the food treated is not likely to be an underestimation. As to Conditions b and c, regional consumption information and

consumption information for significant subpopulations is taken into account through EPA's computer-based model for evaluating the exposure of significant subpopulations including several regional groups. Use of this consumption information in EPA's risk assessment process ensures that EPA's exposure estimate does not understate exposure for any significant subpopulation group and allows the Agency to be reasonably certain that no regional population is exposed to residue levels higher than those estimated by the Agency. Other than the data available through national food consumption surveys, EPA does not have available reliable information on the regional consumption of food to which amitraz may be applied in a particular area.

2. *Dietary exposure from drinking water*. Drinking water was not included in the dietary assessment as it was determined that amitraz is not expected to enter water-bodies or drinking water through the current and proposed uses.

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). Amitraz is currently registered for the following uses that could result in residential exposures: Pet uses from dog collars and spot-on treatments. EPA assessed residential exposure using the following assumptions: There is a potential for residential exposure to amitraz from existing pet uses (dog collars and spot-on treatments), either from applying (handling) the products or from post-application contact with the treated dog. A dermal exposure assessment was performed for adults applying the amitraz pet products. For post-application exposure to treated dogs, a dermal assessment was performed for adults and a dermal and oral (hand to mouth) assessment was performed for children 1-2 years

of age. Handler and post-application inhalation exposure is expected to be negligible and was not quantitatively assessed. EPA did not assess intermediate-term or chronic residential exposures because amitraz is acutely toxic and does not increase in potency with repeated dosing. Residential exposures of all durations can be regarded as a series of repeating one-day exposures based on the current toxicity database for amitraz, which suggests that the central nervous system effects of amitraz are not cumulative, but are a response to each daily dose.

Further information regarding EPA standard assumptions and generic inputs for residential exposures may be found at *http://www.epa.gov/pesticides/trac/science/trac6a05.pdf*.

4. *Cumulative effects from substances with a common mechanism of toxicity*. Section 408(b)(2)(D)(v) of 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 amitraz to share a common mechanism of toxicity with any other substances, and amitraz does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that amitraz 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 *http://www.epa.gov/pesticides/cumulative*.

D. *Safety Factor for Infants and Children*

1. *In general*. Section 408(b)(2)(C) of FFDCA provides that 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 based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA Safety Factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

2. *Prenatal and postnatal sensitivity*. The toxicology database is not complete to assess susceptibility following pre-and/or post natal exposure to amitraz. There was no evidence of increased susceptibility in rats since no developmental toxicity was seen at the highest dose tested in two independent pre-natal developmental toxicity studies in rats. Evidence for susceptibility in rabbits could not be ascertained due to technical deficiencies in the conduct of two independent developmental studies. However, the concern for the lack of susceptibility assessment is lessened because (1) in both studies, developmental effects occurred in the presence of maternal toxicity (one study) or at a dose higher than the dose that caused maternal toxicity (second study); (2) the doses tested in the rabbit studies were higher than the doses tested in developmental study in rats showing that rabbits are not more sensitive than rats. Two reproductive toxicity studies (1-generation and a 3-generation) are available; in the 1-generation study, no reproductive toxicity was seen at the highest dose tested and offspring toxicity was seen in the presence of parental/systemic toxicity. In the 3-generation reproduction study, no reproductive toxicity was seen at the highest dose tested, however, offspring toxicity was

seen at a lower dose than the dose that caused parental/systemic toxicity. Both studies were deemed to be unacceptable due to technical deficiencies in the conduct of these studies. Neurotoxicity was seen in a variety of animal studies and in human subjects and the database does not contain specific neurotoxicity studies.

3. *Conclusion*. The 10x FQPA Safety Factor (for the protection of infants and children) is retained in the form of a database uncertainty factor (UF_{DB}), due to multiple toxicology data deficiencies for amitraz (i.e. reproduction, immunotoxicity, and DNT studies).

i. The toxicity database for amitraz is incomplete, but adequate for purposes of risk assessment. An Extended One-Generation Reproductive Toxicity (EOGRT) study is required for amitraz to evaluate the reproductive, neurotoxic, and immunotoxic potential of amitraz.

ii. Various mammalian species in multiple studies have demonstrated the signs of neurotoxicity for amitraz (i.e., sedation, hypothermia, drowsiness, etc). The DNT study will be a component of the EOGRT study, thus will specifically monitor the potential neurotoxicity of amitraz in targeted testing.

iii. As mentioned in Unit III.D.2., the toxicology database is not complete to assess susceptibility following pre-and/or post natal exposure to amitraz.

iv. There are no residual uncertainties identified in the amitraz exposure databases with regard to dietary or residential exposure and no outstanding exposure data gaps. The dietary assessments are based on conservative, health protective assumptions regarding exposure from food and are designed not to underestimate exposures. Residential exposures resulting from contact with dogs wearing amitraz pet collars is

conservative. The residential risk estimates are based upon protective assumptions of application rate, duration of exposure, and contact with the treated animal. The fraction of application rate transferred, while non-chemical specific, represents the best data available to assess risk from exposures to the amitraz collar and will not underestimate risk. Drinking water was not included in the dietary assessment as it was determined that amitraz is not expected to enter water-bodies or drinking water through the current and proposed uses.

A 10X FQPA safety factor is considered protective for the following reasons: (1) A clear NOAEL was used as the point of departure for risk assessment; (2) the NOAEL was from the most sensitive species; (3) the NOAEL is from an adequate study in humans that examined the most sensitive endpoint (neurotoxicity) seen in the animal data; (4) given the existing animal data, EPA expects that the most sensitive effect found in the EOGRT study will be a neurotoxic one; (5) EPA is applying a 10X intra-species safety factor to account for potential variability in the sensitivity in humans (including potentially greater sensitivity in infants and children than in the adults tested in the human study); and (6) in the 3-generation reproduction study, the only study showing the potential for increased susceptibility in offspring, offspring were less than 4X more sensitive than adult animals; retention of the additional default 10X safety factor for the protection of infants and children means that there will be a 100X factor to account primarily for potential sensitivity in the young even though the available (though incomplete) data show sensitivity in the young of no greater than 4X.

E. *Aggregate Risks and Determination of Safety*

EPA determines whether acute and chronic dietary pesticide exposures are safe by comparing aggregate exposure estimates to the acute PAD (aPAD) and chronic PAD (cPAD). For linear cancer risks, EPA calculates the lifetime probability of acquiring cancer given the estimated aggregate exposure. Short-, intermediate-, and chronic-term risks are evaluated by comparing the estimated aggregate food, water, and residential exposure to the appropriate PODs to ensure that an adequate MOE exists.

1. *Acute risk.* Using the exposure assumptions discussed in this unit for acute exposure, at the 99.9th percentile of exposure, the acute dietary exposure from food to amitraz will occupy 76 % of the aPAD for children 1-2 years old, the population group receiving the greatest exposure.

2. *Chronic risk*. Based on the data summarized in Unit lll.A., there is no increase in hazard with increasing dosing duration. In general, aggregate assessments combine average (chronic) dietary exposures with conservative residential exposures. However, in the case of amitraz, a chronic dietary assessment was not performed since the acute dietary assessment will result in higher estimated exposure levels and will therefore be protective of any chronic aggregate exposures.

3. *Short-term risk*. Short-term aggregate exposure takes into account short-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Amitraz is currently registered for uses that could result in short-term residential exposure. In general aggregate assessments combine average (chronic) dietary exposures with conservative residential exposures. However, in the case of amitraz, a chronic dietary assessment was not performed since the acute dietary assessment will result in higher estimated exposure levels and will therefore be protective

of any chronic exposures. As a screening level aggregate assessment, residential post-application exposures from the small to medium dog collar uses (the residential scenario resulting in the highest estimated exposures) were combined with acute dietary exposures at the 95th percentile of exposure. While aggregation using an average background exposure would more appropriately reflect expected exposures, in the absence of a chronic dietary assessment, use of acute exposures at the 95th percentile of exposure provides a high-end aggregate risk screen.

For children 1-2 years old, the most highly exposed children's subgroup, and for adults, using the exposure assumptions described in this unit for short-term exposures, EPA has concluded that the combined short-term food and residential exposures result in aggregate MOEs of 120 and 450, respectively. For amitraz, MOEs of 100 or greater are not of concern.

4. *Intermediate-term risk*. *Interme*diate-term aggregate exposure takes into account intermediate-term residential exposure plus chronic exposure to food and water (considered to be a background exposure level). An intermediate-term aggregate risk assessment was not conducted because amitraz is acutely toxic and its potency does not increase with repeated dosing. Therefore, the acute and short-term aggregate assessments are protective of intermediate-term aggregate risks anticipated from amitraz exposure.

5. *Aggregate cancer risk for U.S. population*. For the reasons discussed in Unit lll.A., (cancer effects are non-linear and appear at higher doses than acute effects), and Unit lll.E.2., (chronic exposures are lower than acute exposures), the acute aggregate assessment is protective of potential cancer risk.

6. *Determination of safety*. Based on these risk assessments, EPA concludes that there is a reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure to amitraz residues.

IV. Other Considerations

A. *Analytical Enforcement Methodology*

There are two adequate methods, Methods I (designed for animal tissues and milk) and II (designed for plant commodities) available to enforce the proposed tolerances for honey and honeycomb. Both are GLC methods with electron capture detection (ECD), and involve conversion of residues of amitraz and its metabolites containing the 2,4-dimethylaniline moiety to 2,4-DMA using acid and base hydrolysis, respectively. The methods 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 United Nations Food and Agriculture Organization/World Health Organization 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. There are currently no established Codex MRLs for residues of amitraz in/or on honey or honeycomb.

C. *Revisions to Petitioned-For Tolerances*

The petitioner requested a tolerance of 1.0 ppm for amitraz in honey. Based on field trial data (for honey and honeycomb) and using the Organization for the Economical Cooperation and Development (OECD) calculation procedure, the Agency determined that a tolerance of 0.2 ppm for amitraz in honey would be adequate to cover residues from amitraz use in beehives and would harmonize with the European Union (EU) maximum residue level (MRL) for total amitraz in honey.

The registrant did not request a tolerance for honeycomb in its petition to the Agency. However, based on the honeycomb field trial samples and use of the OECD calculation procedure, EPA has determined that a tolerance of 9 ppm is appropriate for honeycomb.

Finally, the Agency has revised the tolerance expression to clarify (1) that, as provided in FFDCA section 408(a)(3), the tolerance covers metabolites and degradates of amitraz not specifically mentioned; and (2) that compliance with the specified tolerance levels is to be determined by measuring only the specific compounds mentioned in the tolerance expression.

V. Conclusion

Therefore, tolerances are established for residues of the insecticide amitraz, (N'-[2,4-dimethylphenyl]-N-[[(2,4-dimethylphenyl)imino]methyl]]-N-methylmethanimidamide), including its metabolites and degredates in or on honey at 0.2 ppm and honeycomb at 9 ppm.

VI. Statutory and Executive Order Reviews

This final rule establishes tolerances under FFDCA section 408(d) in response to a petition submitted to the Agency. 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). Because this final rule has been exempted from review under Executive Order 12866, this final 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) or Executive Order 13045, entitled "Protection of Children from Environmental Health Risks and Safety Risks" (62 FR 19885, April 23, 1997). This final rule 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 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).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the tolerance in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq*.), do not apply.

This final rule directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the

relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled "Federalism" (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled "Consultation and Coordination with Indian Tribal Governments" (65 FR 67249, November 9, 2000) do not apply to this final rule. In addition, this final rule does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (2 U.S.C. 1501 *et seq*.).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA) (15 U.S.C. 272 note).

VII. Congressional Review Act

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), 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 the rule in the **Federal Register**. This action is not a "major rule" as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

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

Dated: March 7, 2013.

Lois Rossi,
Director, Registration Division, Office of Pesticide Programs.

Therefore, 40 CFR chapter I is 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. Section 180.287 is amended by revising paragraph (a) introductory text and by adding, alphabetically, the following commodities to the table in paragraph (a) to read as follows:

§180.287 Amitraz; tolerances for residues.

(a) *General*. Tolerances are established for residues of the insecticide amitraz (N'-[2,4-dimethylphenyl]-N-[[(2,4-dimethylphenyl)imino]methyl]]-N-methylmethanimidamide), including its metabolites and degradates, in or on the commodities in the following table. Compliance with the tolerance levels specified is to be determined by measuring amitraz residues convertible to 2,4-dimethylaniline, expressed as the stoichiometric equivalent of amitraz, in or on the following raw agricultural commodities:

Commodity	**Parts per million**
* * * * *	
Honey	0.2 ppm
Honeycomb	9 ppm
* * * * *	

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