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EPA Registration Division contact: Nancy Fitz

Interregional Research Project Number 4 (IR-4)

PP No: 4E9106

EPA has received a pesticide petition (4E9106) from the Interregional Research Project No. 4 (IR-4), North Carolina State University, 1730 Varsity Drive, Venture IV (Suite 210), Raleigh, NC, 27606, requesting, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180.378 by establishing tolerances for the combined residues of the insecticide cis- and trans-permethrin isomers [cis-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] and [trans-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] in or on the raw agricultural commodities: Arugula at 50 parts per million (ppm); Cress, garden at 50 ppm; Cress, upland at 50 ppm; Dragon fruit (pitaya) at 1.5 ppm; Field corn subgroup 15-22C at 0.05 ppm; Leafy greens subgroup 4-16A at 50 ppm; and Sweet corn subgroup 15-22D at 0.1 ppm.

Remove established tolerances for the combined residues of the insecticide cis- and transpermethrin isomers [cis-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] and [trans-(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] in/on the following food commodities: Corn, field, grain at 0.05 ppm; Corn, pop, grain at 0.05 ppm; Corn, sweet, kernel plus cob with husks removed at 0.10 ppm; Leafy greens subgroup 4A at 20 ppm; Lettuce, head at 20 ppm; and Spinach at 20 ppm.

EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d)(2) of FDDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism.* The qualitive nature of permethrin residues in plants is adequately understood based on the adequate soybean, cabbage, and sweet corn metabolism studies. These studies, conducted to delineate the metabolism of radio-labelled permethrin, all showed similar results. The parent compound (both cis- and trans-permethrin isomers) is the only residue of concern for both tolerance expression and risk assessment.

2. *Analytical method.* Adequate gas chromatography (GC) electron capture detection (GC/ECD) methods are available for enforcing tolerances of permethrin *per se* and are listed in PAM Vol. II (Section 180.378). Method I is a GC/ECD method for determining permethrin in plant matrices

and has a limit of quantitation (LOQ) of 0.05 ppm for each isomer. Method II is a GC/ECD method for determining permethrin in animal matrices that has a LOQ of 0.01 ppm for each isomer. In addition, permethrin is completely recovered using FDA Multiresidue Methods (PAM Vol. I Sections 302 and 304).

3. *Magnitude of residues*. Field residue trials meeting EPA study requirements have been conducted at the maximum label rate on dragon fruit and the residue of permethrin on dragon fruit was evaluated from studies conducted in United States (Florida, Hawaii, and Puerto Rico). Results from the studies demonstrate that the highest permethrin residues found will not exceed the proposed tolerances for Dragon fruit (pitaya) at 1.5 ppm when permethrin is applied following the proposed use directions.

B. Toxicological Profile

1. *Acute toxicity.* Permethrin is classified as having low acute toxicity via the oral, dermal, and inhalation routes. It was found to be a slight eye and dermal irritant, but is not a skin sensitizer. Acute oral rat LD_{50}: 3,580 mg/kg (male) and 2,280 mg/kg (female). Acute dermal rabbit LD_{50}: >2,000 mg/kg. Acute inhalation rat LC50 >2.08 mg/L. Primary eye irritation: irritation 24 to 48 hours all cleared by 72 hours. Acute dermal irritation rabbit: all irritation cleared by 48 hours. Dermal sensitization guinea pig: non-sensitizer. Acute neurotoxicity: no observed adverse effect level (NOAEL): 25 mg/kg/day.

2. *Genotoxicty.* Ames assay: negative. Micronucleus assay: negative. Unscheduled DNA synthesis: negative.

3. *Reproductive and developmental toxicity.* Permethrin has been evaluated for potential developmental effects in the rat and rabbit. No evidence of increased quantitative and/or qualitative susceptibility was seen in these studies. Maternal toxicity included neurological effects such as tremors in the rat and decreased body weights in the rat and rabbit. Increased post-implantation loss, decreased offspring size, and decreased ossification were observed in developmental studies in the rat and rabbit. All effects occurred at maternally toxic doses or above. The potential reproductive toxicity of permethrin was examined in a two-generation reproduction study in the rat. No evidence of increased quantitative and/or qualitative susceptibility was seen in the study. All of the findings in pups were seen at the same doses that caused clinical signs of toxicity and mortality in dams, and the severity of treatment-related effects did not increase in offspring relative to parental animals. The only effect noted in pups was decreased size, occurring at the same dose as tremors in maternal animals.

4. *Subchronic toxicity.* Permethrin has been evaluated for toxicological effects in guideline subchronic toxicity studies. Behavioral changes such as muscle tremors, hyperthermia, aggression, and hypersensitivity, were seen in the toxicological studies which included a subchronic neurotoxicity study in the rat (NOEL 100 mg/kg/day) and subchronic studies in the rat and dog (NOEL of 110 and 100 mg/kg/day, respectively). Tremors were the most common indication of neurotoxicity; however, decreased motor activity from the acute oral study in the rat (Wolansky, *et al*., 2006) provides the most sensitive endpoint ($BMDL_{1SD}$ = 44.0 mg/kg/day).

5. *Chronic toxicity.* A chronic endpoint has not been selected for permethrin because repeated exposure does not result in a point of departure lower than that resulting from acute exposure; therefore, the acute dietary risk assessment is protective of chronic dietary risk.

6. *Animal metabolism.* Based on adequate metabolism studies conducted in ruminants and poultry, the metabolism of permethrin in animals is adequately understood. The residues of concern in animals include cis- and trans-permethrin for purposes of both tolerance expression and risk assessments.

7. *Metabolite toxicology*. The Agency has previously determined that the metabolites of permethrin are not of toxicological concern and need not be included in the tolerance expression.

8. *Endocrine disruption*. Tier 1 studies investigating potential estrogenic or other endocrine effects of permethrin have been conducted. No evidence of such effects was reported in these or in the standard battery of required toxicology studies, which have been completed and found acceptable. Based on these studies, there is no evidence to suggest that permethrin has an adverse effect on the endocrine system.

C. Aggregate Exposure

1. *Dietary exposure.* Tolerances have been established for the residues of permethrin, in or on a variety of raw agricultural commodities. Tolerances, in support of registrations, currently exist for residues of permethrin on the following crops: alfalfa (forage and hay), almond, almond hulls, artichoke (globe), asparagus, avocado, broccoli, Brussels sprouts, cabbage, cauliflower, cherry (sweet and tart), corn (field, including forage, grain, and stover), corn (pop, including grain and stover), corn (sweet, including forage, kernel, and stover), eggplant, pome fruit (crop group 11), garlic (bulb), grain aspirated fractions, hazelnut, horseradish, kiwifruit, leaf petioles (crop subgroup 4B), leafy greens (crop subgroup 4A), lettuce (head), mushroom, onion (bulb), peach, pepper (bell), pistachio, potato, soybean (seed), spinach, tomato, vegetables (cucurbit crop group 9), walnut, and watercress. Permethrin tolerances with regional registrations have been established for collards, papaya, and turnips (tops and roots). Also, tolerances exist for the livestock commodities of grass (forage and hay) as well as cattle (fat, meat, and meat byproducts), goat (fat, meat, and meat byproducts), hog (fat, meat, and meat byproducts), horse (fat, meat, and meat byproducts), poultry (fat, meat, and meat byproducts), sheep (fat, meat, and meat byproducts), egg, and milk (fat). In June 2017, to support Registration Review of permethrin, EPA conducted acute, chronic, and cancer dietary (food and drinking water) exposure and risk assessments using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.18, which uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

i. *Food.*

a. Acute Exposure. A highly-refined probabilistic (Monte-Carlo) acute dietary exposure and risk assessment was conducted on permethrin for all current food uses and drinking water. An acute reference dose (aRfD) of 0.44 mg/kg/day was established based on the lower 95% confidence limit of the benchmark dose value ($BMDL_{1SD}$) of 44 mg/kg/day from a motor activity acute study in rats and an uncertainty factor (UF) of 100 to account for inter-species and intra-species variation. EPA has determined that the Food Quality Protection Act (FQPA) Safety Factor (SF) of 1X is applicable for general U.S. population and children ≥ 6 and FQPA SF of 3X for children < 6 years old. Therefore, the acute population adjusted does (aPAD) for general population and children ≥ 6 years old is equivalent to the aRfD of 0.44 mg/kg/day and aPAD for children < 6 years old is 0.147 mg/kg/day. Permethrin residue estimates used in this assessment include cis- and trans-permethrin, reported by the Biological and Economic Analysis Division (BEAD) of U.S. EPA. The residue estimates are based primarily on the U.S. Department of Agriculture (USDA) Pesticide Data Program (PDP) monitoring data. Both empirical and default processing values were used in the assessment. the acute dietary exposure and risk estimates do not exceed HED's level of concern (less than100% of the acute population-adjusted dose (aPAD)) at the 99.9th exposure percentile for the general U.S. population (2.6% of the aPAD) and all population subgroups. The most highly exposed population subgroup is children 3-5 years old at 20% of the aPAD. FMC concludes that based on adequate % aPAD for all population subgroups there is reasonable certainty that no harm will result from the proposed additional uses of permethrin on dragon fruit.

b. Chronic Exposure. A chronic dietary endpoint has not been selected for permethrin because repeated exposure does not result in a point of departure lower than that resulting from acute exposure; therefore, the acute dietary risk assessment is protective of chronic dietary risk.

ii. *Drinking water.* Modeled surface water estimated drinking water concentrations (EDWCs) were included in the assessments. The EDWCs used in the acute, chronic, and cancer dietary assessments were previously provided by EPA Environmental Fate and Effects Division (EFED) in the following memorandum: "Second Revision Tier II Estimated Drinking Water Concentrations of Permethrin (PC Code # 109701; DP Barcode D324197)" (J. Melendez, D324197, 17-JAN-2006). The Tier II EDWCs of permethrin were calculated using the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS: surface water) and the Screening Concentration in Ground Water (SCI-GROW; ground water) models. The EDWAs were calculated based on a maximum application rate of 2.0 lb. ai/A and were calculated using the "Georgia onion" scenario. The groundwater screening concentrations were lower than the surface water concentrations; therefore, the acute, chronic, and cancer dietary assessments used the surface water EDWCs of 0.00479 ppm, 0.000901 ppm, and 0.000751 ppm, respectively. Water residues were incorporated into the DEEM FCID food categories of "water, direct, all sources" and "water, indirect, all sources."

2. *Non-dietary exposure*. The aggregate residential exposure analyses were based on conservative screening-level assumptions. The residential risk assessments resulted in acceptable MOEs and a clear indication of reasonable certainty of no harm. The short term analyses, all of the route- and product-specific MOEs were greater than 100 and the aggregate MOEs were

greater than 100 for all population subgroups. Based on the above information, FMC concludes that permethrin does not pose a risk due to short- and intermediate-term aggregate exposure.

D. Cumulative Effects

The Health Effects Division of US EPA performed a cumulative risk assessment for the pyrethroids and pyrethrins as a class (D394576, 10/4/2011, K. Whitby). This risk assessment included a dietary exposure analysis in which it was concluded that there were no dietary risks of concern for the pyrethroids and pyrethrins.

E. Safety Determination

1. *U.S. population.* The Tier 3 acute dietary exposure analyses at the 99.9th percentile for the general U.S. Population is 0.011495 mg/kg/day and utilizes 2.6% of the aPAD of 0.44 mg/kg/day. In addition, the acute exposure estimates for population subgroups of concern (infants and children) indicate that the maximum %aPAD or %cPAD utilized is 20% (aPAD). A chronic dietary endpoint has not been selected for permethrin because repeated exposure does not result in a point of departure lower than that resulting from acute exposure. Based on this information FMC concludes that there is reasonable certainty that no harm will result from acute and chronic exposure to permethrin.

2. *Infants and children*.

i. General. In assessing the potential for additional sensitivity of infants and children to residues of permethrin, FMC considered data from developmental toxicity studies in the rat and rabbit, a developmental neurotoxicity study, and a two generation reproduction study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to pregnant animals. Reproduction studies provide information relating to effects from exposure on reproductive organs or reproduction. FFDCA Section 408 provides that the EPA may apply an additional margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and completeness of the database.

ii. Developmental toxicity studies. In the rabbit developmental study, the maternal LOAEL was 600 mg/kg/day based on decreased body weight gain while no maternal NOAEL was observed. The developmental NOAEL was 600 mg/kg/day based on increased post-implantation loss, greater numbers of early and late resorptions, and decreased ossification at LOAEL of 1200 mg/kg/day. In the rat developmental study, the maternal NOAEL was 50 mg/kg/day, based on clinical signs of toxicity receiving the LOAEL of 150 mg/kg/day. The developmental NOAEL was 600 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs receiving LOAEL of 1200 mg/kg/day.

iii. Developmental neurotoxicity study. The developmental neurotoxicity study has been waived for the pyrethroids as a class, including permethrin (TXR# 0055306, E. Scollon, 20-JAN-2010).

iv. Reproductive toxicity study. In the rat reproduction study, parental NOAEL was 50 mg/kg/day based on tremors at the LOAEL of 125 mg/kg/day. There were no developmental (pup) or reproductive effects up to 125 mg/kg/day (highest dose tested).

v. Conclusion. Children 1 to 2 years old had the highest acute dietary (food and drinking water) exposure estimate; therefore, an acute aggregate assessment was conducted for children 1 to <2 years old as well as the general US population. No chronic aggregate assessment was conducted because the acute dietary risk assessment is protective of chronic dietary risk. Using the estimated drinking water and food exposure described above, and based on the completeness and reliability of the toxicity data, the acute aggregate exposure assessments utilized no more than 2.6% of the aPAD for the entire U.S. population and no more than 20% of the aPAD for the most highly exposed population subgroup of children 3-5 years old. Since the EPA generally has no concern for exposures below 100% of the cRfD or aRfD, it may be concluded that there is reasonable certainty that no harm will result to the general U.S. population and infants and children from the acute aggregate exposure to permethrin residues.

F. International Tolerances

The Codex has established MRLs for permethrin on Tea, plucked leaves at 20 ppm, Potato at 0.05 ppm, Celery at 2.0 ppm, Apple, Crabapple, Loquat, Mayhaw, Pear, Asian pear, and Quince at 2.0 ppm, Cherry, sweet and tart at 2.0 ppm, Peach and Nectarine at 2.0 ppm, and Grape at 2.0 ppm.