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TEMPLATE:

[American Spice Trade Association]

[Insert petition number]

EPA has received a pesticide petition ([insert petition number]) from The American Spice Trade Association, 1101 17th Street, NW, Suite 700, Washington, DC 20036, 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 by establishing a tolerance for residues of acetamiprid in or on the following raw agricultural spice commodities: pepper, black at 0.1 parts per million (ppm); and spices from Codex crop group spices, seed that overlap with spices in Crop Group 19: Ambrette, seed; Angelica, seed; Angelica, daharian, seed; Anise, seed; Annatto, seed; Candlebush; Caraway, black, seed; Caraway, seed; Celery, seed; Chervil, seed; Chinese nutmeg tree; Coriander, seed; Cubeb, seed; Culantro, seed; Cumin, seed; Dill, seed; Fennel, seed; Fennel flower, seed; Fenugreek, seed; Grains of Paradise, seed; Guarana; Honewort, seed; Lovage, seed; Mahaleb; Malabar tamarind; Milk thistle; Mustard, black, seed; Mustard, brown, seed; Mustard, white, seed; Nutmeg; Poppy seed; Sesame seed; Wattle seed at 2.0 parts per million (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 metabolism of acetamiprid residue is adequately understood in plants and livestock. Radiolabeled metabolism studies are available for carrot, cabbage, cotton, apple, eggplant, lactating goat, laying hen, and rat. lants, there appears to be little translocation of acetamiprid following foliar application. In cabbage, there was uptake and translocation of acetamiprid to the above-ground portions of the plant following a soil application. Because of the rapid dissipation of acetamiprid in the field, root uptake is not considered to be a likely source of residues in plants. Parent acetamiprid is the predominant residue at >90% of the total radioactive residues (TRR) in three of the five metabolism studies. Confined rotational crop studies showed no residues of acetamiprid at the 30-day plant-back interval. The residue of concern for both tolerance enforcement and risk assessment in primary crops is parent acetamiprid.

2. *Analytical method.* Based upon the metabolism of acetamiprid in plants and the toxicology of the parent and metabolites, quantification of the parent acetamiprid is sufficient to determine residues of concern for enforcement purposes. Approved tolerance enforcement methods for crops are available for acetamiprid, including gas chromatography with electron capture detection (GC/ECD) for vegetables and non-citrus fruits; high performance liquid chromatography with ultraviolet detection (HPLC/UV) for citrus fruits only; and high-performance liquid chromatography with tandem mass spectrometric detection (LC/MS/MS; Method #KP-216R0 and its modification Method #KP-216R1) for vegetables and non-citrus fruits.

3. *Magnitude of residues.* This tolerance is being submitted as part of EPA's Office of Pesticide Programs (OPP) Import Tolerance Pilot Strategy. The strategy relies on data reviews from the Joint Meeting on Pesticide Residues (JMPR), the European Food Safety Authority (EFSA), or a national pesticide authority rather than a *de novo* U.S. review. The evaluation of the residue data submitted to the Joint Meeting on Pesticide Residues (JMPR) to support the establishment of Maximum Residue Levels (MRLs) of acetamiprid for pepper, black, white and the Codex crop group spice, seed is being used to the support the establishment of an import tolerance for acetamiprid on the spices that overlap in the Codex spice, seed and Crop Group 26: Spices in the United States. The evaluation is published in the Joint Meeting on Pesticide Residues Evaluation Report of 2015 for pepper, black, white and of 2019 for spices, seed. (*Pesticide residues in food 2015, Evaluations, Part I -Residues, FAO Plant Production and Protection Paper 226, Pesticides Residues in Spices. Pages 1597-1604. MRID No. 51900702. Evaluations 2019, Part I Residues, Pesticide Residues in Food, Joint FAO/WHO Meeting on Pesticide Residues, Spices, Pesticide Residues. Pages 1747-1766. MRID No. 51900701).*

B. Toxicological Profile

1. *Acute toxicity.* [The acute oral LD- 50 for acetamiprid was 146 mg/kg for female Sprague-Dawley rats and 217 for male rats. The acute dermal LD-50 for acetamiprid was greater than 2000 mg/kg in rats. The acute 4-hour inhalation LC-50 for acetamiprid was greater than 1.15 mg/L, the highest attainable concentration. Acetamiprid was not irritating to the eyes or skin and was not considered to be a sensitizing agent. The NOEL for acute neurotoxicity was 10mg/kg and no evidence of neuropathy was noted. I]

2. *Genotoxicity.* Acetamiprid did not show clear evidence of genotoxic potential. Acetamiprid was not mutagenic under the conditions of a reverse gene mutation assay (with and without metabolic activation) in *Salmonella typhimurium* and *Escherichia coli* (Ames assay).Also, it was not mutagenic in an in vitro mammalian cell gene mutation assay on Chinese hamster ovary (CHO) cells (HPRT locus, with and without metabolic activation).Acetamiprid did not induce unscheduled DNA synthesis (UDS) in either rat liver primary cell cultures or in mammalian liver cells *in vivo.* The compound did not show clear evidence of genotoxic potential. It was positive as a clastogen in an *in vitro* mammalian chromosome aberration assay in Chinese hamster ovary (CHO) cells. However, the *in vivo* chromosomal aberration study does not support the results of the *in vitro* study. Acetamiprid and its metabolites IC-0, IM-1-2, IM-1-4, IM-2-1, and IM-0 tested negative for mutagenicity.

Acetamiprid did not induce a significant increase in chromosome aberrations in bone marrow cells when compared to the vehicle control group and is not a clastogen in the mouse bone marrow micronucleus test.
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3. *Reproductive and developmental toxicity.* In the 2-generation reproduction study, evidence of increased qualitative susceptibility of rat pups was observed. The parental and offspring systemic effects were based on a decrease in mean body weight, body weight gain, and food consumption in the parents and significant reductions in pup weights in both generations. Also observed were reduction in litter size, and viability and weaning indices among F2 offspring as well as significant delays in the age to attain vaginal opening and preputial separation. These offspring observations were considered to be more severe than the parental effects.

In the multi-generation rat reproduction study, a parental NOEL of 280 ppm was established based on decreased body weight, body weight gains, and food consumption. The reproduction NOEL pf 280 ppm was established for reproductive performance and fertility. Evidence of qualitative susceptibility was observed in the 2-generation reproductive study, with the offspring effects (significant reductions in pup weights, reduction in litter size and viability, significant delays in weaning indices and the age to attain vaginal opening and preputial separation) considered more severe than the decrease in parental body weights.

There was no evidence of quantitative or qualitative increased susceptibility of rat or rabbit fetuses to *in utero* exposure of acetamiprid in the developmental studies.

In the developmental neurotoxicity (DNT) study there was also evidence of increased qualitative susceptibility. In this study, the offspring lowest observed adverse effect level (LOAEL) was based on decreased pre-weaning survival [post-natal days (PNDs) 0-1] and decreased maximum auditory startle response in males on PNDs 20 and 60. This was observed in the presence of decreased maternal body weight and body weight gains during gestation. Although offspring and maternal effects were observed at the same doses, the offspring effects were considered to be more severe.

4. *Subchronic toxicity.* In the 3-month dog feeding study a NOAEL of 320 ppm (13/14 mg/kg/day for males/females) was established based on growth retardation and decreased food consumption. In the 3-month rat feeding study a NOAEL of 200 ppm (12.4 and 14.6 mg/kg/day respectively for male and female rats) was established based on BW, BW gain and food consumption at 800 ppm. In the 3-month mouse feeding study a NOAEL of 800 ppm (106.1/129.4 mg/kg/day respectively for male and female mice) was established based on BW, BW gain, decreased glucose, and cholesterol levels, reduced absolute organ weights at 1,600 ppm.

A 13-week dietary neurotoxicity study for acetamiprid established a NOAEL of 200 ppm (14.8 and 16.3 mg/kg for male and female rats) based on reduced body weight, body weight gain and food consumption decreases at 800 ppm. There was no evidence of neurotoxicity.

5. *Chronic toxicity.* Acetamiprid had been classified as "not likely to be carcinogenic to humans" in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July,1999) (TXR 0050331; S.Diwan; 12/11/2001). While there were tumors present in male and female rats from the chronic/carcinogenicity study, the committee concluded the tumors were not treatment-related or appropriate for human risk assessment. The male interstitial cell tumors of the testes occurred at a high background rate in the strain of rats used (Sprague-Dawley) and were not considered treatment related as the incidence did not exceed historical values nor attain significance based on the pair-wise comparison of the dosed groups with the control. The female mammary adenocarcinomas and combined adenomas/adenocarcinomas, pituitary adenomas and combined adenomas/adenocarcinomas were not consistently dose-dependent, nor out of the historical control range; therefore, they were not found to be treatment related. Additionally, tumors were not observed in the mouse carcinogenicity study. No concerns for genotoxicity were identified.

6. *Animal metabolism.* The metabolism of acetamiprid is well understood and the primary animal metabolite is IM-2-1.

7. *Metabolite toxicology*. Metabolites of acetamiprid were examined in a limited study set (acute and subchronic toxicity and *in vitro* mutagenicity tests), and were found to be of equal or lesser toxicity than the parent compound. The toxicology data for acetamiprid is therefore protective of toxicity from the metabolites.

8. *Endocrine disruption*. Acetamiprid does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. Developmental toxicity studies in rats and rabbits and a reproductive study in rats gave no indication that

acetamiprid has any effects on endocrine function. The chronic feeding studies also did not show any long-term effects related to endocrine systems.

C. Aggregate Exposure

1. *Dietary exposure.* Acute and chronic dietary exposure analyses were conducted by the Agency (January 7, 2020, EPA Human Health Risk Assessment) to estimate exposure to potential acetamiprid residues in/on various crops and food handling establishments. The assessment also included residues in meat, milk, poultry, and eggs using the currently established tolerance levels for these commodities. Exposure estimates from drinking water were made based on the PWC Version 1.52 and the Provisional Cranberry Model

i. *Food.* The U.S. population and all population subgroups acute dietary exposure and risk estimates are not of concern. At the 95th percentile of exposure, the risk estimate for the general U.S. population is 40% of the acute population adjusted dose (aPAD). The population subgroup with the highest risk estimate is children 1-2 years old, which is estimated to be 89% of the aPAD. The U.S. population and all population subgroups have chronic dietary exposure and risk estimates that are not of concern. The chronic dietary risk estimate for the general U.S. population is 17% of the cPAD. The chronic dietary risk estimate for the most highly exposed population subgroup, Children 1-2, is 48% of the cPAD. (January 7, 2020 EPA Human Health Risk Assessment)

ii. *Drinking water.* [Residues in surface water estimated by EPA using the PWC model and Provisional Cranberry Model were 37.2 ppb and 88.1 ppb, respectively, for acute exposure and 12.7 ppb for chronic exposure from the PWC model. The ground water concentration was estimated to be 211 ppb for acute and 175 ppb for chronic using the PWC model, For the acute assessment, the EDWC of 211 ppb was used in the DEEM-FCID Model for "water, direct, all sources" and :water, indirect, all sources". For the chronic assessment a value of 175 ppb was used for the same inputs. (January 7, 2020, EPA Human Health Risk Assessment)]

2. *Non-dietary exposure.* [There are no residential post-application concerns for adults and children as MOEs for all age ranges are >100 (January 7,2020 EPA Human Health Risk Assessment).

D. Cumulative Effects

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to acetamiprid and any other substance, and acetamiprid does not

appear to produce a toxic metabolite produced by other substances.

E. Safety Determination

1. *U.S. population.* Based on the current risk assessments, there is reasonable certainty that no harm will result to the general population from exposure to acetamiprid residues from imported commodities of spices.

2. *Infants and children*. The Agency reduced the required 10X FQPA Safety Factor for acetamiprid to 1X based on the following considerations: (1) the toxicology data base is considered complete including developmental, reproductive, and neurotoxicity studies; (2) endpoints and doses for risk assessment were selected based on the effects of concern, i.e., developmental effects in pups following pre-and/or post-natal exposure in the most sensitive species (rat), for which a clear NOAEL and LOAEL were identified; (4) there are no residual uncertainties for pre- and/or post- natal toxicity; (5) the exposure databases (dietary food, drinking water, and residential) are complete, and dietary and residential exposure and risk have not been underestimated. Based on the current risk assessment, there is reasonable certainty that no harm to infants and children will result from aggregate acute or chronic dietary exposure to acetamiprid residues.

F. International Tolerances

There are Codex MRLs established for residues of acetamiprid in or on the following spices. Pepper, black, at 0.1 ppm; Ambrette, seed; Angelica, seed; Angelica, daharian, seed; Anise, se; Annatto, seed; Candlebush; Caraway, black, seed; Caraway, seed; Celery, seed; Chervil, seed; Chinese nutmeg tree; Coriander, seed; Cubeb, seed; Culantro, seed; Cumin, seed; Dill, seed; Fennel, seed; Fennel flower, seed; Fenugreek, seed; Grains of Paradise, seed; Guarana; Honewort, seed; Lovage, seed; Mahaleb; Malabar tamarind; Milk thistle; Mustard, black, seed; Mustard, brown, seed; Mustard, white, seed; Nutmeg; Poppy seed; Sesame seed; Wattle seed at 2.0 parts per million (ppm).