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TEMPLATE:

USDA-Foreign Agriculture Service

3E9060

EPA has received a pesticide petition 3E9060 from USDA Foreign Agriculture Service, 1400 Independence Ave, Washington, DC 20250 proposing, 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 amending the tolerance for residues of fluopyram (*N*-[2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl]-2-(trifluoromethyl)benzamide) in/on imported raw agricultural commodity mango at 1 ppm (there is currently no active U.S. registration for the commodity). 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.* Plant metabolism studies with fluopyram have been performed in grapes, potatoes, and beans after spray applications, on red bell pepper after drip irrigation and wheat after seed treatment. The metabolism in all cases was very similar. The main reactions involved were hydroxylation of the parent compound to AE C656948-7-hydroxy and AE C656948-8-hydroxy, conjugation of the hydroxylated parent compound mainly with sugars, and cleavage of the molecule leading to AE C656948-benzamide, AE C656948-pyridyl-acetic acid (PAA) and AE C656948-carboxylic acid (PCA).

2. *Analytical method.* Fluopyram is the residue of concern in mango. The analytical methods used for residue quantification involve solvent extraction, filtration

and addition of an isotopically labeled internal standard followed by solid phase extraction. Quantitation is by high performance liquid chromatography-electrospray ionization/tandem mass spectrometry (LC-MS/MS).

3. *Magnitude of residues.* The following summary for mango was adapted from the 2017 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) review for the purpose of setting food standards (maximum residue levels for pesticides in food) for fluopyram on mango.

The Meeting reviewed new supervised field trial information and relevant data from supervised field trials provided to the JMPR for mango. Five decline field trials were conducted in Peru and Thailand to measure the magnitude of flupyram residues in/on mango, following two applications of SC formulations containing fluopyram at the critical GAP of 150 g ai/ha, with a minimum application interval of 7 days, and a 7-day pre-harvest interval (PHI). In the trials from Peru, fluopyram residues were also measured in mango flesh, and a median processing factor (flesh:whole fruit ratios) of 0.11 was calculated.

The meeting recommended a maximum residue level of 1 ppm for mango whole fruit.

B. Toxicological Profile

1. *Acute toxicity.* Fluopyram has low acute toxicity to mammals irrespective of the route of exposure (oral, percutaneous or inhalation exposure). It is not a skin sensitizer, it is non-irritating to skin and causes only a minimal reversible redness of the conjunctivae in the rabbit eye. Overall it is classified as Toxicity Classification III. In an acute neurotoxicity study and a follow-up study a NOAEL of 125 mg/kg and 50 mg/kg was established for males and females, respectively based on slight decreases in measures of motor and locomotor activity, clinical signs and decreased body temperature.

2. *Genotoxicty.* Genotoxicity potential was evaluated in a series of tests including *in vitro* and *in vivo* tests. There was no indication of gene mutation either in the presence or absence of metabolic activation in both the bacterial reverse mutation and mammalian gene mutation tests. The *in vitro* chromosome aberration test and the *in vivo* mouse micronucleus test were also both negative. These studies demonstrated that fluopyram has no genotoxic potential.

3. *Reproductive and developmental toxicity.* In the rat two-generation reproduction study, the parental systemic NOAEL was 220 ppm (14.5 mg/kg/day in males, 17.2 mg/kg/day in females) based on clinical pathology changes, increased liver weight, protein droplet nephropathy (males) and centrilobular hypertrophy. The reproductive NOAEL was 1200 ppm in both males and females (82.8 mg/kg/day in males and 93.1 mg/kg/day females), based on no reproductive findings observed in the highest dose tested. The offspring NOAEL was 220 ppm (17.0 mg/kg/day) based on maternal effects leading to secondarily-mediated effects on pup weight and pup weight gain. Also noted was a slight delay in preputial separation and decrease in spleen and thymus weights for F2-pups (both findings considered secondary to pup weight decrease). In a

rat developmental toxicity study, the maternal NOAEL was 30 mg/kg/day, based on a transient reduction on maternal body weight gain and food consumption. The developmental NOAEL was 150 mg/kg/day based on decreased fetal body weight and incidence of two minor variations at both the visceral and skeletal evaluation. In a rabbit developmental toxicity study the NOAEL was 25 mg/kg/day both in the dam (reduced body weight gain and food consumption) and in terms of fetal development (decreased fetal body weight) in the New Zealand White rabbit.

4. *Subchronic toxicity.* Subchronic studies showed that the liver is the major target organ in rats, mice, and dogs. The effects observed were consistent with the induction of hepatic cytochrome P450. In addition to the liver, the thyroid and kidney (males) were also target organs in rats. In the male rat, specific nephropathy (hyaline droplet nephropathy) was observed. The thyroid gland effects were secondary to the liver toxicity. In mice adrenal glands, a lower incidence of ceroid pigment was noted in males, whilst a greater incidence of minimal to slight cortical vacuolation was observed in females. The most sensitive species is considered to be the rat. The dog appeared to be less sensitive than the rat but of similar sensitivity to the mouse. Overall, the lowest NOAEL was observed in the subchronic rat study. In this study the NOAEL for the rat was established at 3.6 and 14.6 mg/kg bw/day in males and females, respectively. In a 90-day study, the NOAEL in the male rats was based on effects in the liver (hepatocellular hypertrophy and vacuolation), the thyroid (hypertrophy of follicular cells) and the specific hyaline droplet nephropathy (and associated effects) observed at the dose level of 12.5 mg/kg/day. The hyaline droplet nephropathy in rats is known to be non-relevant for humans since this specific nephropathy is due to an accumulation of α-2μglobulin in the proximal tubules, a protein that is only found in trace amounts in humans. Therefore, the relevant NOAEL was considered to be 12.5 mg/kg/day since there was no other adverse effect at this dose level. This NOAEL is also comparable with the NOAEL in the 1-year dog study (13.2 mg/kg/day) and the parental and offspring NOAELs (14.5 and 17.0 mg/kg/day, respectively) in the reproduction study.

In a 90-day neurotoxicity study at 0, 100, 500 and 2500 ppm, no evidence of neurotoxicity was observed at any treatment level. Treatment-related findings of general toxicity at the high dose consisted of decreased body weight, total body weight gain and food consumption in males and females, increased cholesterol and triglyceride levels in males and/or females and decreased terminal body weight in females. Also, liver and kidney weights (absolute and relative) were increased in high-dose males and liver weight (absolute and relative) was increased in high-dose females. The only finding at the mid-dose was decreased food consumption in females, which was not associated with any effect on body weight. Based on neurotoxicology endpoints only, a NOAEL of 2500 ppm was established for males and females (164.2 and 197.1 mg/kg for male and female rats, respectively).

In a four-week dermal toxicity study in rats, a NOAEL of 300 mg/kg/day was established based on an increased cholesterol concentration in females, an increased prothrombin time in males and effects on the liver (increased liver weights for males and females associated with hepatic hypertrophy). The increased liver weights and hypertrophy in the high dose group were attributed to hepatic enzyme induction and thus were considered to

be an adaptive response to fluopyram.

5. *Chronic toxicity.* In the rat combined chronic toxicity and carcinogenicity study, retinal atrophy was observed in high dose females. There was marked treatment-related liver toxicity together with nephropathy in the kidney and follicular cell hypertrophy in the thyroid gland. Liver cell tumors (carcinoma and adenoma) were observed in high dose females. The NOAEL for non-neoplastic changes was 150 ppm (equal to 6.0 mg/kg bw per day), based on ocular and thyroid effects in both sexes and findings in the kidney and liver of females at 1500 ppm. The Mechanistic data support a non-genotoxic, threshold phenobarbital-like mode of action resulting in liver cell tumor formation in the female rat. The mode of action for phenobarbital-like inducers is considered to be of limited relevance to humans.

In a mouse carcinogenicity study, the target organs were the liver, kidney and thyroid gland. Nephropathy was observed in the kidney in high dose females. The principal change noted in the liver was centrilobular to panlobular hypertrophy, which was seen in both sexes, and hepatocellular single cell degeneration /necrosis in males. Treatment-related follicular cell hyperplasia was observed in both sexes. Thyroid gland follicular cell adenomas were observed in high dose males. Mechanistic data support a non-genotoxic indirect threshold phenobarbital-like mode of action secondary to liver effects that increased the elimination of thyroid hormones for which a clear NOAEL was established at 30 ppm (equal to 4.2 mg/kg bw per day). And as in the rat, a phenobarbital-like mode of action is considered to be of limited relevance to humans.

6. *Animal metabolism.* Metabolism studies show that fluopyram is rapidly and almost completely absorbed by rats following oral administration by gavage. Fluopyram was extensively metabolized as evidence by the low percentage of eliminated unchanged parent compound. The metabolism of fluopyram in male and female rats was principally oxidative and took place mainly at the ethylene bridge of the molecule. Some cleavage of the rings was observed as was conjugation of several hydroxylated metabolites with glucuronic acid and to a lesser extent with sulfate. The metabolic transformation of the parent compound was generally more pronounced in male rats.

7. *Metabolite toxicology*. Not applicable as parent is the compound of concern.

8. *Endocrine disruption*. Fluopyram showed no indication of endocrine disrupting potential within any of the reproductive, developmental or repeat-dose studies.

C. Aggregate Exposure

1. *Dietary exposure*. The toxicological and exposure database for fluopyram is considered complete. There was no indication of an increased sensitivity of the young in any studies including the reproductive and developmental studies in rats and rabbits. Therefore, the special FQPA safety factor can be reduced to 1X and an uncertainty factor of 100 is adequate to account for inter- and intra- species variability. Acute and chronic Population Adjusted Doses (aPAD and cPAD) are, therefore, the same as the reference doses for the populations and subpopulations of interest. Acute dietary exposure was

expressed as a percentage of the aPAD of 0.50 mg/kg bw/day from a NOAEL of 50 mg/kg bw/day established for females, based on slight decreases in measures of motor and locomotor activity in the acute neurotoxicity study, with an uncertainty factor of 100. Chronic dietary exposure was expressed as a percentage of the chronic Population Adjusted Dose (cPAD) of 0.06 mg/kg bw/day based on an updated NOAEL of 6 mg/kg bw/day in the rat chronic/carcinogenicity study with an uncertainty factor of 100.

Mechanistic studies support the hypothesis that the mouse thyroid and rat liver tumors seen in the chronic studies are from a non-genotoxic indirect threshold mechanism and are not relevant to humans. The CARC has classified fluopyram as "Not Likely to be Carcinogenic to Humans at doses that do not induce cellular proliferation in the liver or thyroid gland; consequently, quantification of cancer risk is not required.

Food and drinking water: Tier 3 acute and chronic dietary risk assessments were conducted to evaluate the dietary exposure of the U.S. population and selected subpopulations to fluopyram residues in food and drinking water. This assessment includes residues from all previous crops, secondary residues in tissues/milk, drinking water, and residues from the new reduced use rates for cereals and canola. Projected Percent Crop Treated (PPCT) were generally based on the market leader method guidance developed by BEAD/EPA. Adjustments were made to the crop residue values to represent the effects of commercial and domestic preparation and processing. The most recent Tier 3 acute and chronic assessments were conducted using DEEM-FCID Ver.4.02 software. Consumption data used in this program were taken from NHANES WWEIA 2005-2010. Acute exposure (95th percentile) for food and drinking water utilizes 9% of the aPAD for the US Population and 25% for Children 1-2, the most highly exposed subpopulation. Chronic exposure utilizes 6.4% of the cPAD for the US Population and 16.3% of the cPAD for Children 1-2 (16.2% for All Infants), the most highly exposed subpopulation(s).

2. *Non-dietary exposure.* The proposed import tolerance on the imported commodity of mango will have no impact on the non-dietary exposure to fluopyram in the U.S.

D. Cumulative Effects

Section 408(b)(2)(D)(v) 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." Fluopyram is a novel fungicide of the chemical class of pyridylethylamides. EPA has not made a common mechanism of toxicity finding as to fluopyram and any other substances and fluopyram does not appear to produce a toxic metabolite produced by other substances.

E. Safety Determination

1. *U.S. population.* Risk assessments for fluopyram are based on a complete and reliable toxicity data package and highly conservative assumptions. Chronic aggregate dietary exposure (food and water) will utilize less than 6.4% of the cPAD for the US

Population. Acute aggregate dietary exposure (food and water) for the U.S. population, utilizes 9% of the aPAD. Non-dietary and aggregate MOEs (food and drinking water) are above the Level of Concern. Therefore, there is a reasonable certainty that no harm will occur to the US Population from aggregate exposure (food, drinking water and non-dietary) to residues of fluopyram**.**

2. *Infants and children*. The toxicological and exposure database for fluopyram is considered complete. There was no indication of an increased sensitivity of the young in any studies including the reproductive and developmental studies in rats and rabbits. Therefore, the special FQPA safety factor can be reduced to 1X and an uncertainty factor of 100 is adequate. Chronic aggregate dietary exposure (food and water) utilizes 16.3% of the cPAD for Children 1-2 (16.2% for All Infants) (below HED's LOC), the most highly exposed subpopulation(s). Acute aggregate dietary exposure (food and water) utilizes 25% of the aPAD for Children 1-2, the most highly exposed subpopulation.

F. International Tolerances

International tolerances have been established for fluopyram for many crops in various countries. The proposed import tolerance for the USA in mango is part of the USDA sponsored ASEAN iMRL pilot project. The establishment of a tolerance for the imported commodity of mango will facilitate global trade.