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TEMPLATE:

[UPL Delaware Inc.]

[1F8976]

EPA has received a pesticide petition (1F8976) from [UPL Delaware Inc.], [630 Freedom Business Center, Suite 402, King of Prussia, PA, 19406] 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

(Options (pick one)

by establishing a tolerance for residues of

[5,6-dihydro-2-methyl-N-phenyl-1,4-oxathiin-3-carboxamide including its metabolites and degradates] in or on the raw agricultural commodities [Crop Subgroup 6-22E and 6-22F at 0.2 parts per million (ppm), field pea forage at 0.4 ppm and field pea hay at 2 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 qualitative nature of the carboxin residues in plants, resulting from seed treatment, is adequately understood as studies have been conducted on several crops. Carboxin is considered systemic in plants. Carboxin sulfoxide was the predominant residue component identified in wheat, beans, and barley plants grown from seeds treated with radiolabeled carboxin. Based on the available total radioactive residue data from a cottonseed metabolism study, a tolerance of 3 ppm in/on cotton gin byproducts for the combined residues of carboxin and its metabolites determined as aniline, has been proposed to be established under 40 CFR §180.301. A confined rotational crop study demonstrated that radiolabeled carboxin residues were taken up by wheat, beets, and lettuce 4 months after treatment.

2. *Analytical method.* [For tolerance enforcement on plant commodities, there are three methods for the determination of the combined residues of carboxin and its metabolites determined as the common moiety, aniline, and expressed as carboxin. Method I is a colometric method recommended for the analysis of carboxin residues in/on corn, peanuts, rice, rice straw, sorghum and soybeans. The LOQ of the method is 0.2 ppm. Method II and its modification, Method A, are both gas-liquid chromatography (GLC) methods. Methods II and A are recommended for analysis of carboxin residues in/on wheat, oats, barley, peanuts, peanut oil and meal, sorghum, cottonseed, and cottonseed oil and meal. The LOQ of the methods is 0.2 ppm. A GLC/MSD method with a lower LOQ was used to analyze samples from corn processing, canola field, and canola processing studies. The LOQ was established at 0.05 ppm for corn forage and fodder, and at 0.025 ppm for corn grain and canola seed.]

3. *Magnitude of residues.* [A total of 12 residue trials were conducted in dry peas with seeds treated at actual rates equivalent to 0.0543 to 0.147 lb a.i./A. For dry pea forage and hay collected 51 to 73 days after planting, maximum residues expressed as carboxin equivalents was 0.323 ppm for forage and 1.45 ppm for hay. For dry pea seed collected 78 to 116 days after planting, all residues expressed as carboxin equivalents were <0.01 ppm. These results support the following proposed tolerances: Crop Subgroup 6-22E and 6-22F at 0.20 ppm, field pea forage at 0.40 ppm and field pea hay at 2.0 ppm]

B. Toxicological Profile

1. *Acute toxicity.* [Carboxin has low oral, dermal and inhalation acute toxicity in laboratory animals. The most sensitive oral LD_{50} was 2588 mg/kg for male rats. The dermal LD_{50} in rabbits was >4000 mg/kg. The inhalation LC_{50} in rats was reported as >4.7 mg/l. In the eye and dermal irritation studies with rabbits, carboxin was considered slightly irritating and not irritating, respectively. Carboxin was not a skin sensitizer in guinea pigs.]

2. *Genotoxicity.* [Carboxin was found to be negative in the bacterial reverse mutation assay (Ames test), *in vitro* mammalian chromosome aberration and in two oral dose *In vivo* mammalian chromosome aberration studies. An *in vivo* mammalian chromosome aberration study with intraperitoneal dose produced a positive result as well as an *in vitro* unscheduled DNA synthesis assay in primary rat hepatocytes. The overall concern for mutagenicity is low since findings in the oral study were negative and the oral route is the most relevant route of administration for risk assessment purposes.]

3. *Reproductive and developmental toxicity.*

[*i. Rat teratology.* Carboxin technical was administered by oral gavage to pregnant rats at dose levels of 0, 10, 90 and 175 mg/kg/day. No adverse effects were observed in either the dams or the fetuses resulting in a maternal and developmental NOEL of 175 mg/kg/day.

ii. Rabbit teratology. Rabbits received carboxin technical by gavage at doses of 0, 75, 375 and 750 mg/kg/day. Abortions were observed in the 750 mg/kg/day group on gestation days 27-28. The abortions are considered to be both maternal and developmental adverse effects resulting in a NOEL of 375 mg/kg/day for both these groups.

iii. Rat reproduction study. Carboxin technical was fed to two generations of male and female rats at dietary concentrations of 0, 20, 200, or 400 ppm for males (0, 1, 10 or 20 mg/kg/day) and 0, 20, 300 or 600 ppm for females (0, 1, 15 or 30 mg/kg/day). The reproductive effects (decreased fertility indices in F2b parents) and offspring effects (decreased pup weight) occurred at higher doses than the parental effects (gross and histopathological changes in the kidneys). The parental NOAEL was 1mg/kg/day (males and females). The reproductive and offspring defined NOAEL was 10 mg/kg/day and 15 mg/kg/day for males and females, respectively.]

4. *Subchronic toxicity.*

[*i. Rat 90-day oral toxicity.* Two 90-day oral toxicity studies with rats are available. In one study, rats received carboxin technical at dietary concentrations of 0, 80, 160 or 240 ppm for males (0, 5.5, 10.5, 16 mg/kg/day) and 0, 80, 160, or 480 ppm for females (0, 6, 12, 37 mg/kg/day). The males and female defined NOAEL were 5.5 and 12 mg/kg/day, respectively, based mainly on kidney histopathology. In the second study, both male and female rats received carboxin technical at dietary concentrations of 0, 200, 800 or 2000 ppm (0, 10, 40, 100 mg/kg/day). No NOAEL was defined for males due to chronic, progressive nephropathy at all treatment levels. A NOAEL of 10 mg/kg/day was defined for females and was also based on chronic nephropathy.

ii. Dog 90-day oral toxicity study. Carboxin technical was administered orally to dogs at dose levels of 0, 5.3, 7.9 or 34.4 mg/kg/day for males and 0, 5.9, 9.0 or 17.7 mg/kg/day for females. No effects were observed in any of the treatment levels resulting in a NOEL of 34.4 and 17.7 mg/kg/day for male and female dogs, respectively.

iii. 28-day dermal toxicity. Male and female rats received daily dermal applications of carboxin technical at doses of 0, 30, 400 or 1000 mg/kg/day. Kidney effects were observed, which included tubular degeneration and tubular mineralization in males. The NOAEL for males and female rats were defined as 400 and 1000 mg/kg/day, respectively.]

5. *Chronic toxicity.* [Carboxin has been tested in chronic studies with dogs, rats, and mice.

i. Dog chronic toxicity study. Male dogs were dosed by capsule at 0, 1.1, 16 and 158 mg/kg/day with carboxin technical. Female dogs were dosed by capsule at 0, 1.3, 15 and 170 mg/kg/day with carboxin technical. Liver enzymes, cholesterol and liver weights were all increased, and treatment related hematological changes were also observed. The hematological changes in dogs included signs of anemia (decreased erythrocytes, hematocrit and hemoglobin; and increased mean corpuscular volume and mean corpuscular hemoglobin). Based on mainly the liver effects, the NOAEL for males was defined as 16 mg/kg/day. The NOAEL for females was defined as 1.3 mg/kg/day based on deceased body weight gains.

ii Rat chronic toxicity/carcinogenicity study. Male rats received carboxin technical at dietary levels of 0, 20, 200 or 400 ppm (0, 0.8, 9.0 and 17 mg/kg/day). Female rats received

carboxin technical at dietary levels of 0, 20, 300 or 600 ppm (0, 1.0, 16 and 34 mg/kg/day). The kidney was the primary target organ with effects demonstrating increased incidence and severity with time. Chronic, progressive nephropathy was observed in addition to other kidney histopathological changes (undifferentiated nephritis, papillary tubular cell mineralization, medullary tubular cell degeneration, pelvic dilation, and papillary-medullary tubular epithelium hyperplasia) Based mainly on the observed kidney effects and decreased body weight, the NOAEL for males was defined as 0.8 mg/kg/day. The NOAEL for females was defined as 1.0 mg/kg/day based on the observed kidney effects.
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iii. Mouse carcinogenicity study. Carboxin technical was administered in the diet of mice at 0, 50, 2500 or 5000 ppm. The equivalent dose was 0, 8.0, 385 and 752 mg/kg/day for males and 0, 9.0, 451 and 912 mg/kg/day for females. Dose-related increases in the incidence of liver centrilobular hypertrophy were observed in the study. However, these increases are considered to be an adaptive rather than an adverse response. The NOAEL for males was defined as 752 mg/kg/day. The NOAEL for females was defined as 9.0 mg/kg/day based on increased mortality.]

6. *Carcinogenicity.* [Carboxin did not produce carcinogenicity in adequately designed chronic studies with rats or mice. Carboxin is categorized as "not likely to be carcinogenic to humans."]

7. *Animal metabolism.* [Rats were dosed orally with carboxin labeled ^{14}C-phenyl. Male and female rats were provided a single low dose at 5 mg/kg and 15 repeated doses at 5 mg/kg. Male and female rats were also provided a single high dose at (150 mg/kg). Carboxin was rapidly and extensively absorbed, metabolized and excreted mostly within 24 hours (64.6-76.5% of the dose). Urine was the major route for excretion of carboxin-derived radioactivity at both the low and high dose, with between 78.3-81.1% of the dose recovered for both sexes at the single and repeated low dose, and 77.0-81.5% recovered at the high dose, by 72 hours. Only 6-12% of the administered dose was excreted in the feces. No major differences in excretion pattern were found between the various treatment groups. Major metabolites identified in the urine were hydroxylated carboxin sulfoxide, 4-acetamidophenol, and 4-acetamidophenol glucuronide; minor metabolites were acetanilide and N-acetylcysteinyl aniline. Carboxin sulfone (oxycarboxin) did not exceed 3.4% of the administered dose in any treatment group. No parent compound (carboxin) was found in the urine. Terminal distribution data showed no significant residual radioactivity (0.4% of the dose or less) in tissues by 72 hours after dosing.]

8. *Metabolite toxicology.* [NA-Remove]

9. *Endocrine disruption.* [A standard battery of toxicity tests has been conducted on carboxin. These tests demonstrated that carboxin has no effect on the endocrine system.]

8. *Immunotoxicity.* [NA-Remove]

C. Aggregate Exposure

1. *Dietary exposure.* [EPA has already included residues of 0.2 ppm for the entire dried

shelled pea and bean (except soybean) Crop Subgroup 6C (this has now been updated to 6-22E and 6-22F), including pea, dry, commodities [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10]. Please note that The Environmental Protection Agency revised the Crop Subgroup 6C crop groupings based on a September 21, 2022 Federal Register Notice which became a final rule on November 21, 2022 (EPA-HQ-OPP-2006-0766 FRL-5031-13-OCSPP).

Since no acute dietary toxicity endpoint for carboxin was identified, acute dietary risk is not of concern, and an acute exposure and risk assessment was not conducted [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10]..

The Health Effects Division carboxin risk assessment team determined that the residues of concern (ROC) for tolerance enforcement and risk assessment in/on crop and livestock commodities should include carboxin and all its metabolites convertible to aniline. Tolerance-level residues for carboxin ROC were used for food commodities in the chronical dietary assessment. The chronic dietary exposure analyses assumed 100% crop treated. [EPA, 2019. Chronic dietary risk assessment Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10].

The chronic analysis incorporated the highest estimated drinking water concentration (EDWC) from ground water exposure (0.0817 ppm). All chronic dietary risk estimates are below the Health Effects Division level of concern [<100% of the chronic population adjusted dose (cPAD)] for all population subgroups. The most highly exposed subgroup is “children 1-2 years old” with a risk estimate at 74% of the cPAD, whereas the risk estimate for the general US population is at 32% of the cPAD [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10].

Cancer: EPA classified carboxin as “not likely to be carcinogenic to humans”; therefore, a cancer dietary assessment was not conducted.]

2. Non-dietary exposure. [There are no residential uses for carboxin [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10].]

D. Cumulative effects.

[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.” 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 carboxin and any other substances. Carboxin may share a common degradate (aniline) with buprofezin. For the purposes of this action, therefore, EPA has not assumed that carboxin have a common mechanism of toxicity with other substances.]

E. Safety determination.

1. *U.S. population.* [Since no acute dietary toxicity endpoint for carboxin was identified, acute dietary risk is not of concern, and an acute exposure and risk assessment was not conducted. The resulting chronic dietary (food and water) exposure estimates are not of concern (<100% cPAD) for the general U.S. population (32% cPAD) or any population subgroups. There are no residential uses. Carboxin is is classified as "not likely to be carcinogenic to humans" and quantification of cancer risk is not required. [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10].]

Based on these assessments, it is concluded that there is a reasonable certainty that no harm will result to the general population from aggregate exposure to carboxin residues.]

2. *Infants and children.* [Since no acute dietary toxicity endpoint for carboxin was identified, acute dietary risk is not of concern, and an acute exposure and risk assessment was not conducted. The resulting chronic dietary (food and water) exposure estimates are not of concern (<100% cPAD) with 74% of the cPAD being related to exposure of children 1-2 years old. There are no residential uses. Carboxin is is classified as "not likely to be carcinogenic to humans" and quantification of cancer risk is not required. [EPA, 2019. Carboxin. Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review. DP Barcode D452645. December 10].]

Based on these assessments, it is concluded that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to carboxin residues.]

F. International tolerances.

[The European Union pesticide database lists maximum residue levels for carboxin on peas as 0.03 ppm.]