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Syngenta Crop Protection, LLC

PP#

EPA has received a pesticide petition (PP#) from Syngenta Crop Protection, LLC, P.O. Box 18300, Greensboro, NC 27419 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 inadvertent residues of fluazifop-p-butyl metabolite 5-(Trifluoromethyl)-2-Pyridone (TFP) in or on the raw agricultural commodity corn forage and grain at 0.01 parts per million (ppm) and corn stover at 0.015 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 fluazifop-p-butyl and 5-(Trifluoromethyl)-2-Pyridone are adequately understood for the purpose of the proposed inadvertent tolerance.]

2. *Analytical method.* [Syngenta has developed and validated new methods for TFP to support this petition including the analytical method GRM044.09A, an updated MRMT (Multi Residue Method Test using QuEChERS), ILV, and Radiovalidation of GRM044.09A]

3. *Magnitude of residues.* [Complete residue data to support the requested inadvertent tolerance are submitted with this petition. The requested tolerances are adequately supported, and all studies were conducted per EPA Test Guidelines 860 Series.]

B. Toxicological Profile

1. *Acute toxicity.* [Fluazifop-p-butyl technical and the end-use formulation have low acute toxicity by oral, dermal and inhalation exposure routes. For fluazifop-p-butyl technical, the oral LD50 in rats is 3680 mg/kg for males and 2451 mg/kg for females. The rabbit dermal toxicity LD50 is >2000 mg/kg and the rat inhalation LD50 is >1.7 mg/l

air. Fluazifop-p-butyl technical is non-irritating to the rabbit eye and slightly irritating to rabbit skin. Fluazifop-p-butyl technical is a weak skin sensitizer.]

2. *Genotoxicity.* [Fluazifop-p-butyl has been tested for its potential to induce gene mutation and chromosomal changes in different test systems. Fluazifop-p-butyl was negative in bacterial reverse gene mutation assays and in mouse lymphoma mammalian cell mutation assays. Fluazifop-p-butyl was negative in in vitro chromosomal aberrations assay in human blood lymphocytes and was negative in the in vivo mouse micronucleus test.]

3. *Reproductive and developmental toxicity.* [Several developmental toxicity studies have been conducted. Based on an HED review of all relevant data, the Agency concluded that the degree of concern is low because selected PODs are protective for observed fetal or offspring effects. The overall developmental NOAEL for the rat developmental toxicity studies is 2.0 mg/kg/day and the LOAEL is 5.0 mg/kg/day based on incomplete and/or delayed ossification.

4. *Subchronic toxicity.* [Fluazifop-p-butyl was evaluated in a number of subchronic studies. In a 90-day rat oral toxicity study the NOAEL was 5 mg/kg/day. Effects at higher doses included decreased body weight and increased liver weights with supportive clinical chemistry findings in males, and renal tubular nephropathy with urinary protein in females. Fluazifop-p-butyl was also evaluated in a 90-day oral toxicity study with hamsters. The NOAEL was 78.3 mg/kg/day, based on decreased body weight and body weight gain as well as food efficiency in males at higher doses levels. Signs of liver toxicity and centrilobular eosinophilia/loss of glycogen were observed in males and females. No dermal toxicity study was conducted with fluazifop-p-butyl; however, in a 21/28 day dermal rabbit study conducted with the racemic mixture fluazifop-butyl, the NOAEL was 100 mg/kg/day. The LOAEL was 500 mg/kg/day based on decreased food consumption and body weight loss leading to mortality in a male.]

5. *Chronic toxicity.* [The Agency has classified fluazifop-p-butyl as not likely to be carcinogenic in humans. In a hamster carcinogenicity study the NOAEL was 12.5 mg/kg/day for males and 12.1 mg/kg/day for females. In a combined carcinogenicity/chronic toxicity study in Wistar rats, in males the LOAEL was 80 ppm (4.15 mg/kg/day) and the NOAEL was 10 ppm (0.51 mg/kg/day) based on increased mortality associated with increased severity of nephropathy during the first year in males. For females the LOAEL was 250 ppm (16.0 mg/kg/day) and the NOAEL was 80 ppm (5.2 mg/kg/day). There was no evidence of carcinogenicity.]

6. *Animal metabolism.* [Metabolism data are available for humans, dogs, rats, and hamsters. The metabolism of fluazifop-p-butyl is adequately understood. Both the racemic mixture fluazifop-butyl and the enriched R-enantiomer fluazifop-p-butyl are rapidly metabolized *in vivo* to the R-enantiomer of fluazifop acid (via a shared achiral intermediate); therefore, the combined database of toxicity studies can be used for hazard assessment.

7. *Metabolite toxicology*. [The major metabolites of fluazifop-p-butyl are fluazifop acid (free and conjugated), 5-trifluromethyl-2-pyridone (TFP) and 2-(4-hydroxyphenoxy) propionic acid (free and conjugated). Fluazifop-p-butyl is rapidly metabolized to fluazifop acid *in vivo*; therefore, the toxicity of fluazifop acid is considered adequately tested in the toxicology database for parent compound. Toxicology data have been submitted for the TFP metabolite to assess the toxicological relevance of this metabolite as a residue of concern. The studies with TFP include acute oral toxicity in rats, 28-day oral toxicity in rats, developmental toxicity in rats, a mutagenicity battery, and metabolism and pharmacokinetics in rats. No adverse effects were observed up to the highest dose tested in the 28-day or developmental toxicity studies. TFP was not genotoxic based on the total findings of the genotoxicity battery. Based on the significantly lower toxicity found in the studies on the TFP metabolite compared to parent fluazifop-p-butyl, the Agency determined that the toxicity data for the parent compound would be protective of the TFP metabolite. Therefore, data from the TFP toxicity studies were not used quantitatively in the risk assessment. However, as an added conservatism, the Agency continued to include TFP as a residue of concern in the risk assessment by using adjustment factors derived from metabolism studies.]

8. *Endocrine disruption*. [There is no indication of endocrine disruption potential from the fluazifop-p-butyl toxicology data. Furthermore, the chemical structure of fluazifop-p-butyl indicates that it is unlikely to disrupt mammalian hormones.]

C. Aggregate Exposure

1. *Dietary exposure.* Acute (Tier I), short-term, and chronic (Tier III) aggregate exposure evaluations were performed for fluazifop-P-butyl using the Dietary Exposure Evaluation Model (DEEM-FCID™, version 4.02) from EPA and consumption data from the USDA NHANES "What We Eat in America" survey, 2005-2010. These exposure assessments included all currently registered uses of fluazifop-P-butyl as well as proposed inadvertent tolerance on field corn to support a plantback interval of 6 months. The Tier I acute assessments incorporated established or proposed tolerances (40CFR180.411) in or on a variety of agricultural commodities including meat, milk and eggs; percent of crop treated values were conservatively estimated to be 100% for all uses in the acute assessments. The Tier III chronic assessments incorporated field trial residue values where fluazifop-P-butyl was applied at the maximum intended use rate and samples were harvested at the minimum pre-harvest interval (PHI) to obtain the maximum expected residues. Estimated percent crop treated (%CT) values were incorporated into the Tier III chronic assessments based upon economic, pest, and competitive pressures. Anticipated residues in meat, milk and eggs were calculated by constructing theoretical nutritionally balanced diets and used in the chronic risk assessments. Empirically derived or DEEMTM (version 7.87) default processing factors were input into the DEEM FCID™ software. Drinking water estimates were included directly into the dietary exposure assessment using the higher of the estimated drinking water concentrations (EDWCs) for surface and ground water.

i. *Food.* Acute Exposure. The acute assessment was performed for all population

subgroups with an acute reference dose (aRfD) of 0.50 mg/kg-bw/day based on a neurotoxicity study in rats with an acute no observed adverse effect level (LOAEL) of 500 mg/kg/day and an uncertainly factor of 100X to account for intra- and interspecies variations. An additional FQPA safety factor of 10X was applied to establish a benchmark MOE of 1,000. For the purpose of the aggregate risk assessment, exposure values were expressed in terms of margins of exposure (MOE), which were calculated by dividing the LOAEL by the exposures for each population subgroup. In addition, exposures were also expressed as percentages of the reference dose (%aRfD). At the 95.0th%-ile of exposures, acute food exposure to the U.S. population resulted in an acute food MOE of 6,769 which was greater than the benchmark MOE of 1,000 and equivalent to 14.8% of the aRfD of 0.50 mg/kg-bw/day. Acute food exposure to the most sensitive subpopulation (children 1-2 years old) resulted in an acute food MOE of 2,219 which was greater than the benchmark MOE of 1,000, and equivalent to 45.1% of the aRfD of 0.50 mg/kg-bw/day.

Chronic Exposure. The chronic assessment was run using DEEM-FCID™ software, average field trial residue values and %CT values. The chronic dietary risk assessment was performed for all population subgroups with a chronic reference dose (cRfD) of 0.0051 mg/kg-bw/day based on a carcinogenicity study in rats with a NOAEL of 0.51 mg/kg/day and an uncertainly factor of 100X to account for intra- and interspecies variations. No additional FQPA safety factor was applied for chronic exposure therefore the benchmark MOE = 100. For the purpose of the aggregate risk assessment, the exposure values were expressed in terms of MOE, which was calculated by dividing the NOAEL by the exposure for each population subgroup. In addition, exposure was expressed as a percent of the chronic reference dose (%cRfD). Chronic food exposure to the U.S. population resulted in a MOE of 862 which is greater than the benchmark MOE of 100 and equivalent to 11.6% of the cRfD of 0.0051 mg/kg-bw/day. Chronic food exposure to children 1- 2 years old, the most exposed population subgroup, resulted in a MOE of 292 which is greater than the benchmark MOE of 100 and equivalent to 34.2% of the cRfD of 0.0051 mg/kg-bw/day.

Cancer. Fluazifop-P-butyl is considered “not likely to be a human carcinogen”. Therefore, no cancer risk assessment was performed.

ii. *Drinking water.* The Estimated Drinking Water Concentrations (EDWCs) were determined for fluazifop-P acid, the acid degradate of parent fluazifop-P-butyl considered as the residue of concern. EDWCs for fluazifop-P acid in surface water and groundwater were determined using the Pesticide Water Calculator (PWC) model (v. 1.52). This drinking water assessment was conducted to assess all currently registered uses.

For surface water, the registered citrus use provided the highest acute EDWC of 68.6 ppb, and the registered use on lettuce provided the highest chronic surface water EDWC of 12.0 ppb. No Percent Cropped Area (PCA) adjustment was made to surface water EDWCs. The acute and chronic groundwater EDWCs were 6.8 ppb and 2.2 ppb, respectively, based upon multiple registered uses. Because surface water EDWCs are higher than groundwater EDWCs, surface water EDWCs will be used for risk assessment

purposes and are considered protective for any groundwater exposure.

Acute Exposure from Drinking Water. The acute surface water EDWC of 68.6 ppb was input directly into the DEEM-FCID™ software as "water, direct and indirect, all sources" to model the acute drinking water exposures. Acute drinking water exposure to the U.S. population resulted in a MOE of 276,702 which is greater than the benchmark MOE of 1,000 and equivalent to 0.4% of the aRfD of 0.5 mg/kg-bw/day. Acute drinking water exposure to the most exposed sub-population (all infants <1 yr) resulted in a MOE of 79,378 which is greater than the benchmark MOE of 1,000 and equivalent to 1.3% of the aRfD of 0.5 mg/kg-bw/day.

Chronic Exposure from Drinking Water. The chronic surface water EDWC of 12.0 ppb was input directly into the DEEM-FCID™ software as "water, direct and indirect, all sources" to model the chronic drinking water exposures. Chronic drinking water exposure to the U.S. population resulted in a MOE of 862 which is greater than the benchmark MOE of 100 and equivalent to 11.6% of the cRfD of 0.0051 mg/kg-bw/day. Chronic drinking water exposure to the most exposed sub-population (all infants, <1 year old) resulted in a MOE of 563 862 which is greater than the benchmark MOE of 100 and equivalent to 17.8% of the cRfD of 0.0051 mg/kg-bw/day.

2. *Non-dietary exposure*. Fluazifop-P-butyl is a selective herbicide used in the post-emergent control of grasses in agricultural, ornamental, residential and recreational (golf course) settings. A residential exposure and risk assessment was performed for Fluazifop-P-butyl uses on turf and ornamentals using the endpoints and uncertainty factors established by the EPA. The fluazifop-P-butyl end-use products are formulated as both liquid concentrates and ready-to-use (RTU) liquids. Homeowners can apply the liquid formulations using a low-pressure hand-wand (LPHW), hose-end sprayer, backpack or watering can. Homeowners can apply the RTU liquids using a hose-end sprayer, trigger-pump sprayer, or watering can. The homeowner handler and residential post-application exposure and risks were determined based on the highest use rates for all lawn and garden products that contain fluazifop-P-butyl. Based on the labels for the various products containing fluazifop-P-butyl, there is a potential for residential handler exposure from consumers making applications to home lawns and ornamentals. There is also a potential for post-application residential exposure to adults and children re-entering treated lawns and to adults and youths playing golf on treated turf. A short-term incidental oral NOAEL of 5.8 mg/kg/day, a short-term dermal NOAEL of 2 mg/kg/day and a short-term inhalation NOAEL of 2 mg/kg/day (all from a developmental toxicity study in rats) were used in these residential risk assessments. Combined short-term MOEs were 200 for adult handlers (backpack sprayer) and 443 for children 1-6 years old (post-application risk); both are above the benchmark MOE of 100 and do not exceed the EPAs level of concern (LOC) of 100.

D. Cumulative Effects

Cumulative Exposure to Substances with a Common Mechanism of Toxicity. 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". The EPA does not have, at this time, available data to determine whether fluazifop-P-butyl has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, the EPA has not assumed that fluazifop-P-butyl has a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population.* Using the conservative assumptions described above, and based on the completeness and reliability of the toxicity data, current, pending and proposed uses of fluazifop-P-butyl resulted in an acute aggregate MOE of 6,607 which is greater than the benchmark MOE of 100 and equivalent to 15% of the aRfD of 0.5 mg/kg-bw/day, LOC = 1000 for the U.S. population. A short-term aggregate MOE of 194 (LOC = 100) and a chronic aggregate MOE of 611 (16% of the cRfD of 0.0051 mg/kg-bw/day, LOC = 100) was determined for the U.S. population.

2. *Infants and children*. Using the conservative assumptions described above, and based on the completeness and reliability of the toxicity data, acute aggregate MOE of 2,201 (45% of the aRfD of 0.5 mg/kg-bw/day, LOC = 1000), a short-term aggregate MOE of 393 (LOC = 100) was determined for children 1-6 years old, and a chronic aggregate MOE of 245 (41% of the cRfD of 0.0051 mg/kg-bw/day, LOC = 100) was determined for children 1-2 years old. The aggregate MOEs for the assessed scenarios for infants and children were determined to be greater LOC (benchmark MOE of 100).

F. International Tolerances

The Codex Alimentarius Commission has established maximum residue limits (MRLs) for fluazifop-P-butyl in or on commodities including almonds, banana, bead fodder, beans (dry), beans (except broad bean and soya bean), head cabbages, caneberries, carrot, celeriac, citrus fruits, citrus dry pulp, coffee beans, cottonseed, currants, edible offal (mammalian), eggplant, eggs, dry field pea, fodder beet, garlic, gooseberry, leaf lettuce, macadamia nuts, mammalian fats (except milk fats), meats (from mammals other than marine mammals), milks, olives for oil production, bulb onion, orange oil, peas (pods and succulent), shelled peas, pecan, pome fruits, potato, poultry fats, poultry meat, edible offal of poultry, shallot, soya bean (dry), soya bean fodder, stone fruits, strawberry, sugar beet, sugar beet molasses, sugar beet dry pulp, sugarcane, sunflower seed, swede, table olives, tomato, garden turnip, and walnuts. The definition of residue for these MRLs is total fluazifop expressed as fluazifop-p-acid.