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UPL NA Inc.

4F9117

EPA has received a pesticide petition (4F9117) from UPL NA Inc., PO Box 12219, Research Triangle Park, NC 27709-2219 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

sodium salt of acifluorfen, sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate in or on the raw agricultural commodity beet, sugar, roots at 0.06 parts per million (ppm) and beet, sugar, tops at 0.06 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 requirements for plant metabolism studies are fulfilled. Adequate studies are available for depicting the metabolism in rice, peanuts, and soybeans. Major metabolites in crops included acifluorfen, acifluorfen amine and several conjugated metabolites. Tolerances for plant commodities are currently expressed in terms of the combined residues of sodium acifluorfen and its metabolites, including the corresponding acid, acifluorfen amine, and the methyl esters of the acid and amine. These data are adequate to cover all registered and proposed crop uses.

2. *Analytical method.* Magnitude of the residues of acifluorfen, acifluorfen ester, acifluorfen amine, and acifluorfen amine ester in sugar beet raw agricultural commodities and sugar beet processed commodities were determined using high performance liquid chromatography analysis employing tandem mass spectrometric direction (LC-MS/MS). The analytical method was ADPEN Method Number AM-2201, "Method for Determination of Residues of Acifluorfen and its Metabolites in Sugar Beet Roots, Tops and Processed Commodities by LC-MS/MS." The validated limit of quantitation (LOQ) was 0.01 ppm for acifluorfen, acifluorfen amine and acifluorfen amine ester, and 0.02 ppm for acifluorfen ester.

3. *Magnitude of residues.* Magnitude of the residue studies were conducted in or on sugar beet raw agricultural commodities (RAC) and processed commodities (PC). Thirteen trials were conducted on sugar beets during the 2021 growing season in NAFTA

Regions 5, 7, 8, 9, 10, and 11. Additionally, data on sugar beet processed commodities were provided from one site in NAFTA Region 5. One application of Ultra Blazer was applied at the nominal rate of 0.375 lb ai/A in a spray volume of 11 to 30 gallons per acre. Additional treated plots were established to generate bulk root samples for the processing phase. One treated plot received one application of sodium salt of acifluorfen at 3 times the treatment rate, 1.129 lbs ai/A. Another treated plot received 5 times the treatment rate, 1.868 lbs ai/A. The broadcast application was applied at BBCH growth stages ranging from 12-14.

Sugar beet top and root raw agricultural commodities were collected at normal crop maturity, corresponding to growth stage BBCH 49 at 57 to 136 days after application. At one trial, additional treated decline RAC samples were collected 103, 117 and 124 days after application (corresponding to -7d, +7d and +14d from commercial maturity) to assess residue decline. All sugar beet RAC samples were collected and frozen on the day of sampling. According to simulated commercial procedures, the sugar beet bulk root samples were processed into refined sugar, molasses and dried pulp processed fractions.

For sugar beet tops, the maximum residue of acifluorfen was 0.0232 ppm. The residues of acifluorfen ester were all <0.020 ppm (LOQ). The residues of acifluorfen amine were all <0.010 ppm (LOQ), and residues of acifluorfen amine ester were all <0.010 ppm (LOQ).

For sugar beet roots, the maximum residue of acifluorfen was 0.0175 ppm. The residues of acifluorfen ester were all <0.020 ppm (LOQ). The residues of acifluorfen amine were all <0.010 ppm (LOQ), and residues of acifluorfen amine ester were all <0.010 ppm (LOQ).

Residues of acifluorfen, acifluorfen ester, acifluorfen amine and acifluorfen amine ester were all <LOQ or non-detect, therefore no decline could be determined.

The results from the processing study show that the mean residues of acifluorfen, acifluorfen ester, acifluorfen amine, and acifluorfen amine ester were <0.010, non-detect (ND), ND and <0.010 ppm, respectively. Due to the low residues in the sugar beet roots collected for processing, concentration factors for refined sugar, molasses and dry pulp were not determined.

B. Toxicological Profile

1. *Acute toxicity.* Sodium Salt of Acifluorfen has low acute toxicity via the oral and dermal exposure routes and is classified as Toxicity Category III for oral and dermal exposure. However, sodium acifluorfen is a severe eye irritant (Toxicity Category I) and moderate dermal irritant (Toxicity Category II). Sodium acifluorfen is not considered a skin sensitizer.

2. *Genotoxicty.* There are no genotoxicity concerns observed in the available toxicity studies. Sodium salt of acifluorfen did not produce gene mutation in unscheduled DNA synthesis assays in primary rat hepatocytes. In sex-linked recessive lethal test in

Drosophila melanogaster, sodium salt of acifluorfen was positive in Y chromosome loss and dominant lethal mutations assays and negative in somatic reversion of white-ivory bithorzx test of Lewis, and sex-linked lethals assay. In an *in vivo* mammalian (rat) chromosome aberration assay, sodium salt of acifluorfen was not mutagenic and there was no increase in clastogenic activity. Similarly in a rodent dominant lethal assay, sodium salt of acifluorfen was not mutagenic.

3. *Reproductive and developmental toxicity.*

i. *Rat Reproduction Study:* In a two-generation reproductive toxicity study in Sprague-Dawley rats, dietary levels of 0, 25, 500, and 2500 ppm sodium salt of acifluorfen (males and female; 0, 1.25, 25, 125 mg/kg/day) were administered. The parental systemic toxicity NOAEL was 1.25 mg/kg/day, with LOAEL of 25 mg/kg/day, based on dilation of tubules in the outer medulla of kidneys in females of both generations. The reproductive NOAEL was 125 mg/kg/day and LOAEL was not observed. The offspring NOAEL was 25 mg/kg/day and the LOAEL was 125 mg/kg/day based on decreased body weight and increased incidence of dilation of the renal pelvis.

ii. *Developmental Toxicity Studies:* In a developmental toxicity study in Sprague-Dawley rats, dietary doses of 0, 20, 90, and 180 mg/kg/day were administered on days 6-19 of gestation. The NOAELs for maternal systemic toxicity and developmental toxicity were 90 mg/kg/day based on decreased fetal body weight and increased incidence of slightly dilated lateral ventricles of the brain. The LOAEL of 180 mg/kg/day for maternal systemic toxic effects was based upon decreased body weight and increased evidence of clinical signs.

In a separate developmental toxicity study conducted in Wistar rats, dietary doses of 0, 30, 60, and 90 mg/kg/day were administered on days 5-19 of gestation. The NOAELs for maternal systemic toxicity and developmental toxicity were 90 mg/kg/day. The LOAELs were not observed and the study noted that the animals could have tolerated a higher dose of sodium salt of acifluorfen.

When sodium salt of acifluorfen was administered to New Zealand White rabbits at doses of 0, 3, 12, 36 mg/kg/day on days 6-29 of gestation, a maternal systemic toxicity LOAEL and developmental toxicity LOAEL were observed at 36 mg/kg/day. The LOAELs were not observed and the study noted that the animals could have tolerated a higher dose of sodium salt of acifluorfen.

4. *Subchronic toxicity.*

i. *Rat 28-day Oral Toxicity Study:* 28-day subchronic study was conducted with sodium salt of acifluorfen in mice at dietary levels of 0, 59, 181, 522, 1286, 2471, 4983 ppm (0, 8.8, 27, 78, 193, 371, 747 mg/kg/day). The NOAEL was 181 ppm (78 mg/kg/day) and the LOAEL was established at 522 ppm (78 mg/kg/day) based on increased liver weight and hisological changes in the liver, multifocal acidophilia, multifocal cell disassociation, multifocal hepatocellular hypertrophy, and diffuse hepatocellular hypertrophy.

ii. Rat 3-month Oral Toxicity Study: A 3-month subchronic study was conducted with sodium salt of acifluorfen in rats at dietary levels of 0, 20, 80, 320, 1250, 2500, 5000 ppm (0, 2, 8, 32, 125, 250, 500 mg/kg/day). The NOAEL was 320 ppm (32 mg/kg/day) and the LOAEL was 1250 ppm (125 mg/kg/day) based on decreases in hematology parameters, increases in liver and kidney weights and increased incidence of hypertrophy of liver cells.

iii. Rabbit 21-day Dermal Toxicity Study: A 21-day dermal toxicity study was conducted with sodium salt of acifluorfen in rabbits at doses of 0, 100, 300 and 1000 mg/kg/day. The high dose level of 1000 mg/kg/day was reduced to 500 mg/kg/day on day 4 of the study by which time 4 rabbits per sex were dead. The NOAEL was 300 mg/kg/day and the LOAEL was 1000 mg/kg/day based on mortality. Skin irritation was noted at the lowest dose tested. By day 8 of the study 19/20 rabbits at the high dose died.

5. *Chronic toxicity.*

i. *Dog 2-Year Feeding Study:* In a 2-year dog study, sodium salt of acifluorfen was fed to groups of dogs at dietary levels of 0, 50, 300, 1800, and 5400 ppm (0, 1.25, 7.5, 45, 135 mg/kg/day). The NOAEL was 1.25 mg/kg/day and the LOAEL was 7.5 mg/kg/day based on coagulation effects.

ii. *Mouse Oncogenicity Studies:* In an 18-month carcinogenicity study, sodium salt of acifluorfen was administered to B6C3F1 mice (60/sex/dose) at dietary levels of 0, 625, 1250 and 2500 ppm (0, 119, 259, 655 mg/kg/day for males and 0, 143, 313, 711 mg/kg/day for females). The NOAEL was not determined and the LOAEL was 119 mg/kg/day based on reduced body weight, increased absolute and relative liver weights, and changes in hematologic parameters, and increases in the incidence of liver tumors and stomach tumors in both sexes.

In a 24-month chronic carcinogenicity study, sodium salt of acifluorfen was administered to CR CD-1 mice (80/sex/dose) at dietary levels of 0, 7.5, 45, 270 ppm (0, 1.125, 6.75, 40.5 mg/kg/day). The highest dose level was initially administered to mice at a dose of 1.25 ppm on study weeks 1 to 16 before being increased to 270 ppm. The NOAEL for systemic toxicity was 45 ppm (6.75 mg/kg/day) and the LOAEL is 270 ppm (40.5 mg/kg/day) based on increased absolute and relative liver weights, and increased relative kidney weights.

iii. Combined Chronic Toxicity/Carcinogenicity Study: In a two-year feeding/oncogenicity study in Fischer 344 rats (73sex/dose) sodium salt of acifluorfen was administered at dietary levels of 0, 25, 150, 500, 2500, 5000 ppm (0, 1.25, 7.5, 25, 125, 250 mg/kg/day). The NOAEL for systemic toxicity was 500 ppm (25 mg/kg/day); the LOAEL was 2500 ppm (125 mg/kg/day) based on reduced body weight, increased absolute and relative liver weights and increased kidney weights, increased incidence of nephritis/pyelonephritis, increased incidence of acidophilic cells in the liver, and related changes in clinical chemistry parameters. No evidence of carcinogenicity was found in this study.

6. *Neurotoxicity* In an acute neurotoxicity study with sodium salt of acifluorfen, rats were treated at dose levels of 0, 293, 440, and 660 mg/kg by weight. The NOAEL was 293 mg/kg and the LOAEL was 440 mg/kg based on decreased (27-44%) ambulatory motor and total motor activities in females during the 0-10 minute interval of Days 0 (treated) and 1. Weight of evidence indicates that acifluorfen is unlikely to be neurotoxic.

7. Immunotoxicity In an immunotoxicity study conducted on rats, dietary administration of sodium salt of acifluorfen was administered at dose levels of 0, 500, 1500, 2500, and 3750 ppm (adjusted to 43.4% ai, 0, 81, 244, 408, and 681 mg/kg/day). They systemic NOAEL was 408 mg/kg/day, the systemic LOAEL was 681 mg/kg/day based on reduced body weights and body weight gains, the immunotoxicity NOAEL was 681 mg/kg/day and the immunotoxicity LOAEL was not observed.

8. Animal metabolism. The nature of the residue in livestock is adequately understood for acifluorfen based on adequate acifluorfen goat and hen metabolism studies. On May 3, 2000, ChemSAC determined that there is no reasonable expectation of finite residues transferring to livestock commodities from treated feed items based on the current use pattern. A weight-of-the-evidence approach was used to arrive at this decision. As a result of this decision, the Metabolism Assessment Review Committee (MARC) did not determine residues of concern for livestock.

The absorption, distribution, metabolism and elimination (ADME) was evaluated in male and female Fischer 344 rats following three oral dosages and an intravenous dosage. Sodium acifluorfen is rapidly and almost completely absorbed into the systemic circulation. The radioactivity recovered in urine and feces in female animals, 96 hours after administration, was 60-82% and 5-23% of the dose, respectively. In contrast, the radioactivity recovered in urine and feces in male rats was 46-58% and 21-41% of the dose, respectively.

No acceptable dermal absorption studies are available for acifluorfen. The dermal absorption factor (DAF) of 18% from structurally-related oxyfluorfen is considered a conservative estimate for sodium salt of acifluorfen.

7. *Metabolite Toxicology.* Data concerning the metabolism of acifluorfen in plants were presented to MARC. MARC concluded the residues of concern in plants are the parent compound (sodium salt - not expected to be present), acifluorfen acid, acifluorfen amine, and the methyl esters of the acid and the amine (D265602, W. Hazel, 05-MAY-2000). Residues of the metabolites are included in the tolerance expression for sodium salt of acifluorfen. No additional metabolite toxicology studies are warranted.

8. *Endocrine disruption*. An evaluation of the potential effects on the endocrine systems of mammals has not been determined; however, no evidence of such effects was reported in the subchronic, chronic, or reproductive toxicology studies described above. There was no observed pathology of the endocrine organs in these studies; therefore, there is no risk of endocrine disruption in humans, livestock, or wildlife. There is no

evidence that acifluorfen causes endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure.* Permanent tolerances for residues of sodium salt of acifluorfen are expressed in terms of sodium salt of acifluorfen, sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate, and its metabolites (the corresponding acid, methyl ester, and amino analogues) [40 CFR §180.383(a)] in/on Berry, low growing, subgroup 13-07G; peanut; rice, grain; soybean, seed; soybean, vegetable, edible podded; soybean, vegetable, succulent shelled. Additionally, time limited tolerances are established for restudies of the herbicide sodium salt of acifluorfen and its metabolites (the corresponding acid, methyl ester, and amino analogues in/on sugar beet roots and leaves [40 CFR §180.383(b)]. The time limited tolerances expire on 12/31/2024. Adequate enforcement methods are available for the determination of sodium salt of acifluorfen residues of concern (ROC) in/on plant commodities. The current enforcement methods determine sodium acifluorfen, acifluorfen, acifluorfen amine, and any other compounds that can be converted to acifluorfen methyl ester or the HFBA derivative.

In the 2023 risk assessment conducted by EPA, the Agency established the relevant toxicity endpoint for sodium salt of acifluorfen at an acute reference dose of 0.20 mg/kg/day (females 13-49 years of age) and 2.9 mg/kg/day for all other populations. The chronic reference dose was established at 0.013 mg/kg/day.

i. *Food.* In July of 2023, the EPA conducted an unrefined acute and unrefined chronic (food and drinking water) risk assessment to evaluate the proposed tolerances and uses on edamame (vegetable soybean) and crop group expansion and use on Low-Growing Berry, Subgroup 13-07G. This risk assessment included use on sugar beets at the default residue level of 0.1 ppm per the Section 18 emergency exemption temporary tolerance on sugar beets (roots and leaves) set to expire December 31, 2024. Since the July 2023 EPA risk assessment included a tolerance for sugar beets at a higher level than UPL NA Inc.'s proposed tolerance in the current petition, UPL NA Inc. asserts that the July 2023 EPA risk assessment can be used to evaluate the proposed permanent tolerance on sugar beets. The acute risk assessment used tolerance-level residues and 100% crop treated (%CT) assumptions. Maximum estimated drinking water concentrations (EDWCs) from the Environmental Fate and Effects Division (EFED) were also included. Tolerance level residues along with Health Effects Division's (HED) default processing factors were used where appropriate. The chronic risk assessment used tolerance-level residues, 100%CT, and HED's default processing factors. A food only analysis for both acute and chronic risk assessments demonstrated that water is the primary contributor to aggregate (food + water) dietary exposure to sodium salt of acifluorfen.

ii. *Drinking water.* The EPA's dietary assessment conducted in 2023 used the drinking water residues provided by EFED in the memorandum "Acifluorfen

Drinking Water Assessment for Registration Review" (D465170, D465202, B. Kierman, 10/05/2022). Water residues were incorporated in the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) into the food categories "water, direct, all sources" and "water, indirect, all sources."

Based on groundwater modeling results from Pesticide Root Zone Model – Ground Water (PRZM-GW), the maximum EDWC for sodium acifluorfen for acute, chronic and 30 year exposure assuming maximum application rates for current uses is 146 ppb for the 1 in 10 year peak, annual average, and 30 year annual average concentrations.

iii. *Food + Drinking Water.* The EPA's 2023 acute and chronic dietary exposure assessments were conducted using the DEEM-FCID, Version 4.02, which incorporates 2005-2010 consumption data from U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

2. *Non-dietary exposure*. There are no residential uses of sodium salt of acifluorfen; therefore, direct exposures in residential settings are not expected for adults and children. However, non-occupational indirect exposure resulting from spray drift from agricultural applications onto residential areas may occur. In an occupational setting, applicators may be exposed while handling the pesticide prior to application as well as during application. Occupational post-application exposure and risk estimates for soybeans indicate that short- and intermediate-term margins of exposure (MOEs) are not of concern on day of application. There is also potential for post-application exposure for workers re-entering treated fields. Exposure to workers is limited by the use of Personal Protective Equipment and a Restricted Entry Interval (REI) of 48 hours.

3. *Cancer Dietary Exposure Assessment:* Sodium salt of acifluorfen is classified as "likely to be carcinogenic to humans at high enough doses to cause the biochemical and histopathological changes in livers of rodents, but unlikely to be carcinogenic at doses below those causing these changes" (Kidwell, 2003, TXR #0052014). According to the June 17, 2015 *Sodium Acifluorfen. Draft Human Health Risk Assessment for Registration Review*, the chronic reference dose (RfD) of 0.013 mg/kg/day is protective of both cancer and non-cancer effects. In the EPA's 2023 acute and chronic dietary exposure assessment, chronic dietary (food and water) risk estimates associated with the use of sodium acifluorfen did not exceed the Agency's level of concern (>100% cPAD) for any population subgroup. As the use of sodium acifluorfen did not exceed the Agency's level of concern for chronic dietary risk and the chronic reference dose is protective of both cancer and non-cancer effects, UPL believes that the use of sodium acifluorfen on sugar beets at the tolerance level proposed in this petition will not exceed the Agency's level of concern for cancer risk as well.

D. Cumulative Effects

EPA has not made a common mechanism of toxicity finding as to sodium salt of acifluorfen and any other substances, and sodium acifluorfen does not appear to produce a toxic metabolite produced by other substances. EPA has grouped sodium acifluorfen with PPO inhibitors and intends to apply the Pesticide Cumulative Risk Assessment: Framework for Screening Analysis to determine if the available toxicological data for sodium acifluorfen suggests a candidate for establishing a common mechanism group (CMG) with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be considered by the EPA to provide an initial screen for multiple pesticide exposure. As a common mechanism of toxicity finding has not been made for sodium acifluorfen, for purpose of this tolerance action, therefore, sodium salt of acifluorfen does not have a common mechanism of toxicity with other substances.

E. Safety Determination Risk assessments for sodium salt of acifluorfen are based on a complete and reliable toxicity data package for the metabolite and pesticidal active ingredient sodium salt of acifluorfen and conservative assumptions.

1. *U.S. population.* a. Acute risk. The acute dietary exposure from food and water to sodium salt of acifluorfen will occupy 3.9% of the acute population adjusted dose (aPAD) for Females 13 to 49 years of age according to the EPA's July 2023 unrefined acute (food and drinking water) risk assessment to evaluate previously proposed tolerances and uses on edamame (vegetable soybean) and crop group expansion and use on Low-Growing Berry, Subgroup 13-07G. Tolerances in EPA's July 2023 unrefined acute (food and drinking water) risk assessment were inclusive of tolerances for sugar beets at a higher level than the tolerances proposed in this petition. The risk assessment was based on upper-end (95th percentile) exposure estimates and no crop treatment refinements were utilized. For the US population, the estimated acute dietary exposure accounted for <1% of the aPAD (2.9 mg/kg/day).

b. Chronic risk. The aggregate exposure for existing crops would utilize 24% of the cPAD for the General Population and 87% of the cPAD for all infants (<1 year old), the most highly exposed population subgroup. Generally, exposures below 100% of the RfD are of no concern because it represents the level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risk to human health. Thus, there is reasonable certainty that no harm will result from aggregate exposures to sodium salt of acifluorfen residues.

2. *Infants and children*. The toxicological database for sodium acifluorfen is complete with regard to pre- and postnatal toxicity, neurotoxicity, and immunotoxicity; there are no residual uncertainties. Additionally, the dietary exposure assessments previously conducted by EPA for sodium acifluorfen were based on conservative, health-protective assumptions that ensure that exposures to sodium acifluorfen were not underestimated. Developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats are available. The acute dietary endpoint of 2.9 mg/kg /day for the general population derived from the acute neurotoxicity study in rats and the chronic dietary endpoint of 0.013 mg/kg/day for the general population derived from the rat reproduction study are both protective of infants and children in addition to the general

population. Based on this analysis, HED recommended during Registration Review of sodium salt of acifluorfen that the 10x Food Quality Protection Act (FQPA) Safety Factor (for the protection of infants and children) be reduced to 1x.

FFDCA section 408 provides that EPA may apply an additional uncertainty factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on current toxicological data requirements, the database for sodium salt of acifluorfen relative to pre- and post-natal effects for children is complete. Conservative assumptions utilized to estimate aggregate dietary exposures of infants and children to sodium salt of acifluorfen demonstrated that <1% of the aPAD and 87% of the cPAD would be utilized for the highest exposed group, infants (<1 year old). Therefore, it may be concluded that there is reasonable certainty that no harm will result to infants and children from aggregate exposures to sodium salt of acifluorfen.

F. International Tolerances

There are no Codex, Mexican, or Canadian MRLs for sodium salt of acifluorfen on sugar beets.