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Glufosinate-Ammonium: Tolerance Petition for Rice Commodities, revised June 2024

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[BASF Corporation]

[1E8952]

EPA has received a pesticide petition 1E8952 from BASF Corporation, 26 Davis Drive, Research Triangle Park, North Carolina 27709 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 180.473 by amending tolerances for residues of the herbicide glufosinate-ammonium, including its metabolites and degradates. Compliance with the tolerance levels specified below is to be determined by measuring the sum of glufosinate-ammonium (butanoic acid, 2-amino-4-(hydroxymethylphosphinyl)-monoammonium salt), and its metabolites, 2-acetamido-4-methylphosphinico-butanoic acid and 3-methylphosphinico-propionic acid, expressed as 2-amino-4-(hydroxymethylphosphinyl) butanoic acid equivalents in or on the following raw agricultural plant commodities: by amending tolerance in or on rice, grain from 1.0 parts per million (ppm) to 0.9 (ppm), and by removing tolerance on rice, hull at 2.0 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 uptake and metabolism of glufosinate in primary crops is adequately understood. Radiolabeled studies have been conducted in various plants all showing similar results. The relevant residues are parent glufosinate-ammonium and MPP (3-methylphosphinico-propionic acid) in conventional plants and additionally NAG (N-acetyl glufosinate, 2-acetamido-4-methylphosphinico-butanoic acid) in glufosinate-tolerant plants.

2. *Analytical method.* Glufosinate-ammonium and its two metabolites 2-acetamido-4-methylphosphinico-butanoic acid (NAG) and 3-methylphosphinico-propionic acid (MPP), expressed as 2-amino-4-(hydroxymethylphosphinyl) butanoic acid equivalents (glufosinate acid equivalents) are the residues of concern in plant commodities required for analysis based on the metabolic profile. The analytical methods for crops matrices involve water 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.* Residue trials were conducted across the major regions of rice production in the U.S. The treatment regime was selected to represent the use pattern that is the most likely to result in the highest residues. Glufosinate-ammonium derived residues did no exceed 0.74 ppm in rice grain when sampled at 70 days or more after the last treatment. No concentration of the residues occurred when rice whole grain was processed into polished grain and bran.

B. Toxicological Profile

1. *Acute toxicity.* Glufosinate-ammonium has been classified as US-EPA toxicity category III for acute oral, dermal, and inhalation toxicity, and for eye irritation. Glufosinate-ammonium is not a dermal irritant (toxicity category IV) nor is it a dermal sensitizer. The oral LD50 is 4010 mg/kg in male rats and 3030 mg/kg in female rats.

2. *Genotoxicty.* Based on results of a complete genotoxicity database, there is no evidence of mutagenic activity in a battery of studies, including: an Ames assay, an in vitro mammalian cell gene mutation assays, a bacterial DNA damage and repair assay, an in vivo mouse bone marrow micronucleus assays, and an unscheduled DNA synthesis assay.

3. *Reproductive and developmental toxicity.* In a developmental toxicity study, groups of 20 pregnant female Wistar rats were administered glufosinate-ammonium by gavage at doses of 0, 0.5, 2.24, 10, 50 and 250 mg/kg/day from days 7 to 16 of pregnancy. The NOAEL for maternal toxicity is 10 mg/kg/day; the LOAEL is 50 mg/kg/day based on vaginal bleeding and hyperactivity in dams. In the fetus, the NOAEL is 50 mg/kg/day, based on dilated renal pelvis observations at the LOAEL of 250 mg/kg/day. In a developmental toxicity study, groups of 15 pregnant female Himalayan rabbits were administered glufosinate-ammonium by gavage at doses of 0, 2.0, 6.3, or 20.0 mg/kg/day from days 7 to 19 of pregnancy. In maternal animals, decreases in food consumption and body weight gain were observed at the 20 mg/kg/day dose level. The NOAEL for maternal toxicity was 6.3 mg/kg/day and that for developmental toxicity was 20 mg/kg/day**.**

In a multi-generation reproduction study, glufosinate-ammonium was administered to groups of 30 male and 30 female Wistar/Han rats in the diet at concentrations of 0, 40, 120, or 360 ppm. The LOAEL for systemic toxicity is 120 ppm based on increased kidney weights in both sexes and generations. The systemic toxicity NOAEL is 40 ppm. The LOAEL for reproductive/developmental toxicity is 360 ppm based on decreased numbers of viable pups in all generations. The NOAEL is 120 ppm.

In a developmental neurotoxicity study, groups of 25 bred female rats were fed glufosinate-ammonium at doses of 0, 200, 1000 or 4500 ppm in the diet. Body weights and food consumption were decreased at 1000 and 4500 ppm. No effects were seen in treated animals for the functional observation battery, developmental landmarks, grip strength, startle response or learning and memory. Motor activity was increased at the mid and high dose. The NOAEL for developmental neurotoxicity was determined to be 200 ppm.

4. *Sub-chronic toxicity.* In a sub-chronic oral toxicity study, glufosinate-ammonium was administered to 10 NMRI mice/sex/ dose in the diet at levels of 0, 80, 320 or 1,280 ppm (equivalent to 0, 12, 48 or 192 mg/kg bw/day) for 13 weeks. Significant ($p< 0.05$) increases were observed in serum aspartate aminotransferase and in alkaline phosphatase in high-dose (192 mg/kg/ day) males. Also observed were increases in absolute and relative liver weights in mid-(48 mg/kg/day) and high-dose males. The no observed adverse effect level (NOAEL) is 12 mg/kg/day, the lowest observed adverse effect level (LOAEL) is 48 mg/kg/day based on the changes in clinical biochemistry and liver weights.

5. *Chronic toxicity.* In a dog 1 year study, technical glufosinate-ammonium was fed to male and female beagle dogs for 12 months in the diet at levels of 2.0, 5.0, or 8.5 mg/kg/day. The NOAEL is 5.0 mg/kg/day based on clinical signs of toxicity, reduced weight gain and mortality 8.5 mg/kg/day.

In a combined chronic toxicity/oncogenicity study, glufosinate-ammonium was administered to 50 Wistar rats/sex/dose in the diet for 130 weeks at dose levels of 0, 40, 140, or 500 ppm (mean compound intake in males was 0, 1.9, 6.8, and 24.4 mg/kg/day and for females was 0, 2.4, 8.2 and 28.7 mg/kg/day, respectively). A dose-related increase in mortality was noted in females at 140 and 500 ppm, whereas in males increased absolute and relative kidney weights were noted at 140 ppm and 500 ppm. The NOAEL was considered to be 40 ppm in females and 140 ppm in males. No treatment-related oncogenic response was noted.

Additionally, a rat oncogenicity study was performed in which glufosinate-ammonium was administered to Wistar rats (60/sex/group) for up to 24 months at 0, 1,000, 5,000, or 10,000 ppm (equivalent to 0, 45.4, 228.9, or 466.3 mg/kg/day in males and 0, 57.1, 281.5, or 579.3 mg/kg/day in females). The LOAEL for chronic toxicity is 5,000 ppm, based on increased incidences of retinal atrophy; the NOAEL is 1000 ppm (equivalent to 45.4 mg/kg/day for male rats and 57.1 mg/kg/day for females. Under the conditions of this study, there was no evidence of carcinogenic potential.

In a mouse oncogenicity study, glufosinate-ammonium was administered to 50 NMRI mice/sex/dose in the diet at dose levels of 0, 80, 160 (males only) or 320 (females only) ppm for 104 weeks. The NOAEL for systemic toxicity is 80 ppm (10.82/16.19 mg/kg/day in males/females (M/F)), and the LOAEL is 160/320 ppm (22.60/ 63.96 mg/kg/day in M/F), based on increased mortality in males, increased glucose levels in males and females, and

changes in glutathione levels in males. No increase in tumor incidence was found in any treatment group.

6. *Animal metabolism.* Studies conducted in rats using ^{14}C-glufosinate-ammonium have shown that the compound is poorly absorbed (5-10%) after oral administration and is rapidly eliminated primarily as the parent compound. The highest residue levels were found in liver and kidney tissues.

The metabolic profile and the quantitative distribution of metabolites were very similar in both goat and hen. The vast majority of the dose was excreted, primarily as parent compound. The very limited residues found in edible tissues, milk and eggs were comprised principally of glufosinate and 3-methylphosphinico-propionic acid (MPP), with lesser amounts of N-acetyl-glufosinate (NAG) and 2-methylohosphinico-acetic acid (MPA).

7. *Metabolite toxicology*. Additional testing has been conducted with the major metabolites, 3-methylphosphinico-propionic acid, and N-acetyl-L-glufosinate. Based on sub-chronic and developmental toxicity study results, lower toxicity was observed for the metabolites as compared to the parent compound, glufosinate-ammonium.

8. *Endocrine disruption*. No evidence of estrogenic or other endocrine effects have been noted in any of the toxicology studies that have been conducted with this product, and there is no reason to suspect that any such effects would be likely.

C. Aggregate Exposure

1. Dietary exposure. The toxicological and exposure database for glufosinate is considered complete. Tolerances have been established (40CFR part 180.473) for the combined residues of glufosinate-ammonium and metabolites in or on a variety of raw agricultural commodities. No appropriate toxicological endpoint attributable to a single exposure was identified in the available toxicity studies. EPA did not, therefore, establish an acute reference dose (aRfD) for any population subgroup except females 13-49 years old. An acute RfD of 0.0063 mg/kg/day was established for the females 13-49 years old subgroup, based on a developmental NOAEL of 6.3 mg/kg/day in the rabbit and a 100x uncertainty factor (10x inter- 10x intra-species extrapolation) and a 10x data uncertainty factor. EPA determined that the Special FQPA uncertainty factor would be 1X for the acute dietary risk assessment based on conclusions of the HIARC and the complete residue and environmental fate data bases. The developmental LOAEL (20 mg/kg/day) was based on increased fetal death in the presence of maternal toxicity. There was no qualitative or quantitative indication of increased susceptibility in the prenatal developmental toxicities in rats and rabbits or in the 2-generation reproductive study in rats with parent compound or metabolites of concern

Food and drinking water: An unrefined acute dietary risk assessment using tolerance level residues and default processing factors for glufosinate ammonium with an EDWC of 201 ppb showed that the acute dietary risk estimates are not of concern (i.e. <100% aPAD) for the relevant population subgroup, females 13-49 years old with 26% of the aPAD (95th Percentile) using DEEM-FCID (ver.4.02). The same evaluation with CAREs NG (Ver 1.2.0) showed that the unrefined acute aggregate (food + water) dietary risk estimates was 26% for females 13-49 years old. In both acute dietary assessments drinking water constitutes >60% of the aggregate risk.

The chronic dietary exposure assessment for glufosinate ammonium is refined using anticipated residues based on average residue levels from field trial studies. For livestock commodities, anticipated residues were also used. Average %CT information and processing factors, where available, were incorporated into the assessment. The chronic dietary risk assessment for glufosinate ammonium with an EDWC of 24.4 ppb showed that the chronic dietary risk estimates are not of concern (i.e. <100% cPAD) for all population subgroups, with the highest exposed population subgroup, all infants <1 year-old, at 42% of the cPAD and the U.S. Population at 11% of the cPAD using DEEM-FCID (ver. 4.02). The same evaluation with CAREs NG (Ver 1.2.0) showed that the chronic aggregate (food + water) dietary risk estimates was 40% for the highest exposed subpopulation, all infants <1 year old. In both chronic dietary assessments water constitutes approximately 75% of the aggregate risk.

2. *Non-dietary exposure*. There is a potential for exposure to glufosinate-ammonium from non-dietary turf uses. EPA recently assessed the residential handler and residential post-application exposures for use of glufosinate-ammonium in turf (January 8, 2021, DP Barcode D456135). The residential post-application exposures calculated by EPA were included above in the short-term aggregate risk assessment.

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." Glufosinate-ammonium is a novel herbicide and EPA has not made a common mechanism of toxicity finding as to glufosinate-ammonium and any other substances and glufosinate-ammonium does not appear to produce a toxic metabolite produced by other substances.

E. Safety Determination

1. *U.S. population.* Risk assessments for glufosinate ammonium 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 15% of the cPAD for the US Population. Acute aggregate dietary exposure (food and water) for females 13-49 years old, utilizes 26% 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 glufosinate ammonium.

2. *Infants and children*. The toxicological and exposure database for glufosinate ammonium is considered complete. Chronic aggregate dietary exposure (food and water) utilizes 42.2% of the cPAD for all infants (< 1 year old), the most highly exposed subpopulation. Since no acute endpoint was determined for any population other than females 13-49, the acute aggregate exposure was not determined for infants or children.

EPA generally has no concerns for exposures below 100 percent of the RfD, because the RfD represents the level at or below which daily aggregate exposure over a lifetime will not pose appreciable risks to human health. Therefore, there is a reasonable certainty that no harm will occur to infants and children from aggregate exposure to residues of glufosinate-ammonium.

F. International Tolerances

Tolerances have been established for glufosinate ammonium in/on rice, grain by Japan at 0.3 ppm, Indonesia at 0.9 ppm, Singapore at 0.9 ppm and Thailand at 0.9 ppm