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BASF Corporation

EPA has received a pesticide petition (Insert Petition Number) from BASF Corporation, 26 Davis Drive, Research Triangle Park, NC 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 180.490 by establishing a tolerance for residues of imazapic (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1-H-imidazol-2-yl]-5-methyl-3-pyridinecarboxylic acid in or on the raw agricultural commodity rice, grain at 0.05 parts per million (ppm) and rice, bran at 0.2 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 metabolic pathway of imazapic is understood and is similar in a range of different crops including Bermuda grass, sugarcane and peanuts (a legume). Parent imazapic and the hydroxymethyl metabolite M715H001 (CL 263284) were identified as major components of the total residue. Imazapic is metabolized via oxidative hydroxylation of the 5-methyl substituent to form the 5-hydroxymethyl metabolite M715H001 (CL263284), which in immature plants and mature leaves is subsequently conjugated with glucose to form metabolite M715H002 (CL189215).

2. *Analytical method.* BASF Method SOP-PA.0288 was used for the analysis of imazapic and its metabolites in all rice specimens. Final detection was accomplished with LC-MS/MS with

a LOQ of 0.010 mg/kg for each analyte. Analytical method procedural recovery samples were analysed together with the field specimens covering the fortification range from 0.010 to 0.10 mg/kg for all analytes in rice (grain with hull, brown rice, milled rice, straw and bran). Method validation of this method was previously submitted to EPA.

3. *Magnitude of residues. i. Rice.* Imazapyr was applied at labeled rates in nine field trials which were conducted in Vietnam and The Philippines. Total residues of imazapic and its relevant metabolites in/on whole rice (grain with hull) were <0.026 to 0.031 mg/kg at 80-104 days after last application. Using the OECD MRL Calculator, residue values of imazapic (sum of parent plus M715H001 and M715H002) for rice grain results in a calculated MRL of 0.04 mg/kg; however, it is proposed to set the US tolerance to 0.05 mg/kg based on the currently existing Codex MRL of 0.05 mg/kg for imazapic on rice grain.

Rice processed commodities from the treated plots were also analyzed, and residues of total imazapic in/on brown rice, polished rice and bran were <0.026-0.041, <0.026-0.029 and <0.026-0.101 mg/kg, respectively. As residue levels in rice bran derived from rice grain treated at the 1x label rate exceed the proposed tolerance of 0.05 mg/kg for rice grain, the OECD MRL Calculator was used to calculate a tolerance for rice bran leading to the proposed tolerance of 0.2 mg/kg.

ii. Ruminants. The dietary burden of imazapic for ruminants was calculated according to the EPA's Maximum Reasonably Balanced Diet using tolerance level values for rice grain and rice bran along with all registered feed items. The addition of rice commodities did not affect the current dietary burden for ruminants according to the MRBD; therefore, no new tolerances are proposed for livestock commodities.

iii. Poultry. The dietary burden of imazapic for poultry and swine was calculated according to the EPA's Maximum Reasonably Balanced Diet using tolerance level values for rice grain and rice bran along with all registered feed items. The addition of rice commodities did not affect the current dietary burden for poultry or swine according to the MRBD; therefore, no new tolerances are proposed for livestock commodities.

B. Toxicological Profile

1. *Acute toxicity.* Imazapic technical is considered to be non-toxic (toxicity category IV) to the rat by the oral route of exposure. In an acute oral toxicity study in rats, the LD_{50} value of imazapic technical was greater than 5,000 milligrams/ kilograms body weight (mg/kg bw) for males and females. The results from an acute dermal toxicity study in rabbits indicate that imazapic is slightly toxic (toxicity category III) to rabbits by the dermal route of exposure. The dermal LD_{50} value of imazapic technical was greater than 2,000 mg/kg bw for both male and

female rabbits. Imazapic technical is considered to be nontoxic (toxicity category IV) to the rat by the respiratory route of exposure. The 4-hour LC_{50} value was greater than 5.52 mg/L (analytical) for both males and females. Imazapic technical was shown to be non-irritating to rabbit skin (toxicity category IV) and minimally irritating to the rabbit eye (toxicity category III). Based on the results of a dermal sensitization study, imazapic technical is not considered a sensitizer in guinea pigs.

2. *Genotoxicity.* Imazapic technical was tested in a battery of *in vitro* and *in vivo* genotoxicity assays measuring several different endpoints of potential genotoxicity. Collective results from these studies indicate that imazapic does not pose a mutagenic or genotoxic risk.

3. *Reproductive and developmental toxicity. i.* The developmental toxicity study in Sprague Dawley rats conducted with imazapic technical showed no evidence of teratogenic effects in fetuses and no evidence of developmental toxicity. Thus, imazapic is neither a developmental toxicant nor a teratogen in the rat. In the rat developmental toxicity study with imazapic technical, the no observed adverse effect level (NOAEL) for maternal toxicity and developmental toxicity was 1,000 mg/kg bw/day, the highest dose tested.

ii. Results from a developmental toxicity study in New Zealand White rabbits with imazapic technical also indicated no evidence of teratogenicity or developmental toxicity. Thus, imazapic technical is neither a developmental toxicant nor a teratogen in the rabbit. In the rabbit developmental toxicity study, the NOAEL for maternal toxicity was 350 mg/kg bw/day, based on decreased food consumption and body weight gain at 500 mg/kg bw/day, the next highest dose tested. The NOAEL for developmental toxicity was determined by EPA to be 500 mg/kg bw/day; the excessive mortality in dams at 700 mg/kg bw/day (the highest dose tested) resulted in too few fetuses that were available for evaluation.

iii. The results from the two-generation reproduction toxicity study in rats with imazapic technical support a NOAEL for parental toxicity of 20,000 ppm (or approximately 1,205 mg/kg bw/day in males and 1,484 mg/kg bw/day in females, calculated from food consumption data), the highest concentration tested. The NOAEL for growth and development of the offspring is also 20,000 ppm, or approximately 1,205 mg/kg bw/day in males and 1,484 mg/kg bw/day in females. Results from the reproduction study and the developmental toxicity studies conducted with imazapic technical show no increased sensitivity to developing offspring as compared to parental animals, because the NOAELs for growth and development of offspring were equal to or greater than the NOAELs for parental toxicity.

4. *Subchronic toxicity. i.* A short-term (21-day) dermal toxicity study in rabbits was conducted with imazapic technical. No dermal irritation or abnormal clinical signs were observed

at dose levels up to and including 1,000 mg/kg bw/day (highest dose tested), supporting a NOAEL for dermal irritation and systemic toxicity of 1,000 mg/kg bw/day.

ii. In a subchronic (13-week) dietary toxicity study in rats with imazapic technical, no signs of systemic toxicity were noted, supporting a NOAEL of 20,000 ppm (or approximately 1,552 mg/kg/day for males and 1,728 mg/kg/day for females, calculated from food consumption data), the highest concentration tested. The requirement for a subchronic dietary toxicity study in non-rodents is satisfied by the one-year dietary toxicity study in dogs.

5. *Chronic toxicity. i.* A one-year dietary toxicity study was conducted with imazapic technical in Beagle dogs at dietary concentrations of 0, 5,000, 20,000, and 40,000 ppm. In this study, the NOAEL for systemic toxicity was less than 5,000 ppm or approximately 158 mg/kg bw/day (137 mg/kg bw/day for males and 180 mg/kg bw/day for females), calculated from food consumption data, based on a slight skeletal myopathy, characterized by degeneration/necrosis of single fibers (minimal severity) and lymphocyte/macrophage infiltration in skeletal muscle, in males and females, and slightly decreased serum creatinine in females at 5,000 ppm (lowest concentration tested). However, during a 2018 review of imidazolinone herbicides, the EPA changed the endpoint for the chronic dog study to reflect current practices in hazard evaluation. It was determined that the new NOAEL for systemic toxicity was 501 and 534 mg/kg bw/day in males and females, respectively. The LOAEL is 1,141 and 1,092 mg/kg bw/day in males and females, respectively, based on decreased body weight, increased incidence of salivation and emesis, changes in hematological parameters, red blood cell morphology findings, changes in clinical chemistry parameters, gross pathology in bone marrow, and histopathological findings.

The skeletal myopathy observed at 5,000 ppm was considered of minimal toxicological significance because the limited presence and the minimal severity of skeletal myopathy were evident in only a few fibers out of hundreds evaluated per section per animal. Further, these focal myopathies of minimal severity were not consistently diagnosed in all skeletal muscles sites examined per dog (i.e., vastus and abdominal muscles, diaphragm and esophagus). Moreover, no clinical observations indicative of muscle dysfunction were noted in any animal in the study. Finally, although the skeletal myopathy noted at 40,000 ppm (highest concentration tested) was associated with increases in creatine kinase, aspartate aminotransferase and lactate dehydrogenase, no statistically or biologically significant increases in these serum enzymes were noted during the study period for animals in the 5,000 ppm group. As such, the minimal myopathy diagnosed microscopically at 5,000 ppm was not considered to impair or adversely affect the functional capacity of the affected skeletal muscles.

ii. In a 2-year chronic dietary oncogenicity and toxicity study in rats conducted with imazapic technical, the NOAEL for oncogenicity and chronic systemic toxicity was 20,000 ppm

(approximately 1,029 mg/kg bw/day in males, 1,237 mg/kg bw/day in females, calculated from food consumption data), the highest concentration tested.

iii. An 18-month chronic dietary oncogenicity and toxicity study in mice with imazapic technical supports a NOAEL for oncogenicity and for chronic systemic toxicity of 7,000 ppm (or approximately 1,134 mg/kg bw/day in males, 1,422 mg/kg bw/day in females, calculated from food consumption data), the highest concentration tested.

The EPA has classified imazapic as a group E carcinogen (evidence of noncarcinogenicity for humans) based on the absence of treatment-related tumors in acceptable carcinogenicity studies in both rats and mice.

6. *Animal metabolism.* The rat, goat and hen metabolism studies indicate that the qualitative nature of the residues of imazapic in animals is adequately understood.

In the rat metabolism study conducted with radiolabeled imazapic (BAS 715 H, CL 263,222), urinary excretion was the primary elimination route with 94% to 102% of the radioactivity excreted in the urine. The major component in the urine and feces was the unchanged parent compound.

Lactating goats were orally treated using radiolabeled imazapic. Imazapic was mainly eliminated from the goat through urine and feces. HPLC of goat urine showed essentially unchanged imazapic, while residues in feces were comprised of imazapic and low levels of hydroxymethyl metabolites M715H001 (CL 263,284). There were no detectable radiolabeled imazapic-derived residues in milk during or after treatment, nor in tissues except kidney 20 hours after the last dose. The ^{14}C-residue in the high-dose kidney (0.05 mg/kg) was predominantly parent imazapic with low levels of metabolite M715H001 (CL 263,284, 8% TRR, <0.01 mg/kg) and two unknowns, each ≤0.02 mg/kg.

A ruminant metabolism study was also conducted with the radiolabeled imazapic hydroxymethyl metabolite M715H001 (CL 263,284). During treatment, TRR in the daily blood and milk samples were less than 0.01 mg/kg, regardless of the treatment dose levels. The TRR in liver, muscle, and omental fat were less than 0.01 mg/kg, regardless of the dose level. Analysis of the kidney extract showed that 9% (<0.01 mg/kg) of the extractable TRR was CL 263,284.

A metabolism study was performed on hens using radiolabeled imazapic. Total recovery of radioactivity in urine and feces was 90.6% and 95.2% for the low and high doses, respectively.

Residues in all tissues (liver, kidney, muscle, skin with adhering fat), blood and eggs were <0.01 mg/kg, the validated detection limit.

A poultry metabolism study was also conducted with the radiolabeled imazapic hydroxymethyl metabolite M715H001 (CL 263,284). Total recovery of radioactivity in urine and feces was 85.3% and 88.6% for the low and high doses, respectively. Residues in all tissues, liver, kidney, muscle, skin with adhering fat, blood and eggs, were less than 0.01 mg/kg, the validated detection limit.

7. *Metabolite toxicology*. Metabolism studies in grass, peanuts and sugarcane indicate that the only significant metabolites are the hydroxymethyl resulting from hydroxylation of the methyl group at the 5-position of the pyridine ring, (±)-2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-5-hydroxymethyl-3-pyridinecaroxylic acid, and the conjugate resulting from glucosylation at the hydroxyl group. The hydroxymethyl metabolite was also identified in minor quantities in the rat metabolism study and in the goat metabolism study. No additional toxicologically significant metabolites were detected in the plant or animal metabolism studies.

8. *Endocrine disruption*. Collective organ weight data and histopathological findings from the two-generation rat reproductive study, as well as from the subchronic and chronic toxicity studies in three different animal species, demonstrate no apparent estrogenic effects or treatment-related effects of imazapic on the endocrine system.

C. Aggregate Exposure

1. *Dietary exposure.*

i. *Food.*

a. Acute Dietary Exposure. An acute dietary assessment is not necessary because no acute dietary endpoint was selected based on the absence of an appropriate endpoint attributable to a single dose of imazapic.

b. Chronic Dietary Exposure.

The proposed endpoint for use in the chronic dietary assessment was obtained from the Draft Human Health Risk Assessment for Registration Review (Sep 26, 2018):

Summary of toxicological dose and endpoint in chronic dietary assessment				
Exposure/scenario	Point of departure	Uncertainty/ FQPA safety factor	RfD, PAD	Study and toxicological effects
Chronic dietary (all populations)	NOAEL = 501-534 mg/kg/day (M/F). LOAEL = 1141/1092 mg/kg/day (M/F)	UF = 100 FQPA SF = 1x	Chronic RfD = 5.0 mg/kg/d cPAD = 5.0 mg/kg/d	Chronic toxicity (dog)

A Tier 1 assessment of potential chronic dietary exposure was performed for the proposed import tolerances for use of imazapic on rice. The assessment was done using both DEEM™ and CARES NG, incorporating the current tolerances as listed in 40 CFR 180.490 on peanut, soybean seed, sugarcane, tissues of cattle, sheep, goats, and horses, and milk and the proposed tolerances for rice grain and rice bran. For this Tier 1 analysis, tolerance values were used for rice grain at 0.05 mg/kg, rice bran at 0.2 mg/kg; peanut at 0.1 mg/kg; soybean seed at 0.4 mg/kg; sugarcane at 0.03 mg/kg; fat of cattle, sheep, goats, and horses at 0.1 mg/kg; kidney of cattle, sheep, goats, and horses at 1.0 mg/kg; meat byproducts, except kidney of cattle, sheep, goats, and horses at 0.1 mg/kg; meat of cattle, sheep, goats, and horses at 0.1 mg/kg; and milk at 0.1 mg/kg.

ii. *Drinking water*. Drinking water residues at an estimated drinking water concentration (EDWC) of 14 µg/L, i.e., the maximum level estimated by EPA, as reported in the 2001 Federal Register notice (66 FR 66325) were included in a dietary assessment using DEEM™ and CARES NG. A proposed tolerance for an imported commodity would have no impact on the exposure due to drinking water.

iii. *Aggregate dietary.* Chronic dietary exposure analyses (food and water) for the overall U.S. population and population subgroups, including infants and children, were compared to the chronic Population Adjusted dose (cPAD) of 5.0 mg/ kg b.w./day. Results of the chronic dietary analyses for all population subgroups examined were at or below 0.11% of the cPAD. Exposure estimates for children 1-2, the most highly exposed subpopulation, were only 0.005621mg/kg b.w./day (or 0.11% of the RfD); therefore, the results of the chronic dietary assessment demonstrate a reasonable certainty of no harm from the proposed and existing uses of imazapic.

Results for imazapic chronic dietary exposure (food and water) considering all current, pending, and proposed tolerances using DEEM-FCID and CARES NG

Population Subgroups	DEEM FCID Exposure Estimate (mg/kg bw/day)	CARES NG Exposure Estimate (mg/kg bw/day)	% cPAD
U.S. Population	0.00123	0.00123	0.02
All Infants (< 1 year old)	0.002737	0.002737	0.05
Children (1-2 years old)	0.005621	0.005621	0.11
Children (3-5 years old)	0.003304	0.003305	0.07
Children (6-12 years old)	0.001907	0.001907	0.04
Youth (13-19 years old)	0.001004	0.001004	0.02
Adults (20-49 years old)	0.000875	0.000875	0.02
Adults (50+ years old)	0.000821	0.000821	0.02
Females (13-49 years old)	0.000878	0.000878	0.02

2. *Non-dietary exposure*. Residential aggregate exposure assessments are not required because the only source of potential imazapic exposure in the U.S. is via the diet and drinking water.

D. Cumulative Effects.

Imazapic belongs to the imidazolinone class of compounds a class comprised of a number of registered herbicides. The herbicidal activity of the imidazolinones is due to the inhibition of acetohydroxyacid synthase (AHAS), an enzyme only found in plants. AHAS is part of the biosynthetic pathway leading to the formation of branched chain amino acids. Animals lack AHAS and this biosynthetic pathway. This lack of AHAS contributes to the low toxicity of the imidazolinone compounds in animals. We are aware of no information to indicate or suggest that imazapic has any toxic effects on mammals that would be cumulative with those of any other chemical.

E. Safety Determination

1. *U.S. population.* Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to the general population from the aggregate exposure to imazapic from the existing uses and proposed import tolerances.

2. *Infants and children.* Based on this risk assessment, BASF concludes that there is a reasonable certainty that no harm will result to infants or children from the aggregate exposure to imazapic from the existing uses and proposed import tolerances.

F. International Tolerances. The Codex MRL for imazapic on rice grain is currently 0.05 mg/kg. It is proposed to harmonize with this MRL for the US import tolerance of rice from Asia.

The MRL for rice grain in the EU is also 0.05* mg/kg.