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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 180.500 by establishing a tolerance for residues of imazapyr 2-[4,5-dihydro-4-methyl-4-(1-methylethyl)-5-oxo-1*H*-imidazol-2-yl]-3-pyridinecarboxylic acid in or on the raw agricultural commodity on rice, grain at 0.06 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 imazapyr is understood and is similar in a range of different crops including Bermuda grass, Imidazolinone-Resistant corn, clover and soybean. Parent imazapyr was identified as major component of the total residue.

i. Bermuda grass. Radiolabelled imazapyr (pyridine-6-^{14}C-imazapyr), was applied to established Bermuda grass. A single application was made at the nominal rate of 1.5 lbs a.i./A. Samples of Bermuda grass were collected for analysis at 0, 4, 10, 15 and 21 days after treatment. The majority of residues were extracted with acidified methanol (86 – 97% TRR). The predominant residue, accounting for 78 to 97% TRR, was the parent compound, imazapyr. Metabolites CL 240000 and CL 247087 each accounted for $\leq$ 10%TRR while CL 9140 was present at a maximum of 12% TRR. The study demonstrated that imazapyr is metabolized slowly in Bermuda grass and the major residue in the foliage is imazapyr.

ii. Imidazolinone-Resistant corn. Radiolabeled imazapyr was applied once to maize plants in two plots at 0.025 lb a.i./A and 0.071 lb a.i./A. Imazapyr was the only major residue found in maize grains or in plants of different growth stages. Any metabolite observed was only present at insignificant concentrations in samples taken after the day of application. Thus, imazapyr is the only relevant residue in maize. Additionally, extraction of maize oil with hexane showed that residues of imazapyr did not accumulate in that lipophilic matrix.

iii. Clover. Radiolabeled imazapyr was applied once as an aqueous solution to established clover at 1.5 lb a.i./A (1680 g a.i./ha). Imazapyr was the major residue in clover plants, accounting for

68 to 99% TRR. Metabolites CL 9140, CL 240000 and CL 247087 each accounted for insignificant proportions of the residue below 10% TRR. Thus, the study demonstrates that imazapyr is the only relevant residue in clover.

iv. Soybean. Radiolabeled imazapyr was applied once as an aqueous solution to established CV127-9 soybean at 0.096 lb ai/A (107 g ai/ha). Imazapyr underwent significant metabolism; however, the parent molecule was the most abundant component of the residue in all matrices except straw and pods. Imazapyr is significantly metabolized in soybean, but no metabolites occur that would be metabolites of concern. Thus, the study demonstrates that imazapyr is the only relevant residue in soybean.

2. *Analytical method.* BASF Method SOP-PA.0288 was used for the analysis of imazapyr of all rice specimens. Final detection was accomplished with LC-MS/MS with a LOQ of 0.010 mg/kg. 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 9 field trials which were conducted in Vietnam and Philippines. Residues of imazapyr in/on whole rice were <0.01 to 0.031 mg/kg at 80-104 days after last application.

Rice processed commodities were also analyzed, and residues of imazapyr in/on brown rice, polished rice, bran and rice straw were <0.01-0.036, <0.01-0.029, <0.01-0.12 and <0.01-0.013 mg/kg, respectively.

ii. Ruminants. Not relevant to this import tolerance since the residues in rice grain will not affect the livestock dietary burden for ruminants.

iii. Poultry. Not relevant to this import tolerance since the residues in rice grain will not affect the livestock dietary burden for poultry.

B. Toxicological Profile

1. *Acute toxicity.* Imazapyr has low toxicity via the oral, dermal and inhalation routes of exposure. It is not irritating to the skin and showed no dermal sensitization potential (Buehler Method). An eye irritation study demonstrated irreversible corneal opacity.

2. *Genotoxicity.* Imazapyr showed no genotoxic potential in a battery of studies on gene mutation (Ames Assay, CHO/HGPRT Mutation Assay) and other genotoxic effects (*in vitro* CHO cell chromosome aberration assay, dominant lethal assay, unscheduled DNA synthesis (UDS) in primary rat hepatocytes and mouse micronucleus).

3. *Reproductive and developmental toxicity. i.* For a rat developmental toxicity study at doses of 0, 100, 300, or 1,000 mg/kg body weight/day (b.w./day), the only clinical sign of toxicity was salivation in gravid dams at 1,000 mg/kg b.w./day. The No-Observed-Adverse-Effect Level (NOAEL) for maternal toxicity is 300 mg/kg b.w./day. There were no developmental findings in this study up to the limit dose of 1,000 mg/kg b.w./day, the highest dose tested (HDT).

ii. For a rabbit development toxicity study at doses of 0, 25, 100, and 400 mg/kg b.w./day, the maternal and developmental NOAEL is 400 mg/kg b.w./day, the HDT. Doses were based on pilot range-finder study, which tested at 0, 250, 500, 1,000, and 2,000 mg/kg b.w./day. The only toxic effect observed was increased salivation at 1,000 and 2,000 mg/kg b.w./day.

iii. A 2–generation rat reproduction study at doses of 0, 1,000, 5,000, or 10,000 ppm yielded a NOAEL of 10,000 ppm highest concentration tested (HCT) (equivalent to 738 mg/kg b.w./day for males, 933.3 mg/kg b.w./day for females).

4. *Subchronic toxicity. i.* A 90–day dietary study in rats at doses of 0, 15,000, or 20,000 ppm resulted in a NOAEL of 20,000 ppm, the HCT (approximately 1,695 mg/kg b.w./day for males, 1,785 mg/kg b.w./day for females).

ii. A 21–day rabbit dermal toxicity study at doses of 0, 100, 200, or 400 mg/ kg b.w./day resulted in the NOAEL of 400 mg/kg b.w./day, the HDT.

5. *Chronic toxicity. i.* A 1–year chronic toxicity study in dogs at doses of 0, 1,000, 5,000, or 10,000 ppm yielded a NOAEL of 10,000 ppm, the HCT (equivalent to 250 mg/kg b.w./day).

ii. A 2–year chronic toxicity/ carcinogenicity study in rats at doses of 0, 1,000, 5,000, or 10,000 ppm provided NOAELs for both systemic toxicity and oncogenicity of 10,000 ppm, the HCT (approximately 500 mg/kg b.w./day for males, 640 mg/kg b.w./day for females).

iii. An 18–month oncogenicity study in mice at doses of 0, 1,000, 5,000, or 10,000 ppm provided NOAELs for both systemic toxicity and oncogenicity of 10,000 ppm, the HCT (equivalent to 1,500 mg/kg b.w./day).

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

i. Rat. Results from a rat metabolism study indicated that imazapyr was rapidly absorbed and excreted by 7 days post-dosing, with the majority (90%) of the administered ^{14}C-label eliminated in the urine within 48 hours. Metabolite characterization studies showed that essentially all the test material was excreted unchanged. Two minor metabolites were detected in the urine or feces of treated rats; however, their contribution combined was less than or equal to 0.5% of the administered dose. An additional 12 unidentified metabolites were isolated, but they contributed less than 3% of the total dose.

ii. *Ruminant*. Goats were dosed with radiolabeled imazapyr at 17.7, 42.5, or 47 mg/kg dietary equivalents for 7 days. As assessed for goats receiving the 17.7 or 42.5 mg/kg doses, TRR in fat, liver, and leg and loin muscle were nondetectable (<0.05 mg/kg). The TRR in milk was a maximum of 0.01, 0.02, and 0.02 mg/kg for the three goats, respectively, while the TRR in kidney was 0.08, 0.11, and 0.08 mg/kg, respectively. Of these residues, parent imazapyr accounted for 50–66% of the TRR in milk and 82–95% of the TRR in kidney. No metabolites were identified which require regulation.

iii. *Poultry.* Hens were dosed with radiolabeled imazapyr at 0, 1.98 and 9.72 mg/kg. TRR in the egg samples was less than the validated detection limit of 0.01 mg/kg. Residues in blood, skin with adhering fat, muscle, liver and kidney tissues taken at 22 hours after the last dose were all less than the validated detection limit of 0.01 mg/kg. The results of this study clearly show that orally administered imazapyr was rapidly eliminated by the hen as unchanged parent compound and that imazapyr related residues do not accumulate in eggs or the edible tissues of poultry. Based on these metabolism results, and expected dietary burden in poultry, a poultry feeding study is not necessary.

7. *Metabolite toxicology*. There were no metabolites identified in plant or animal commodities which require regulation.

8. *Endocrine disruption*. The collective data from the 2-generation rat reproduction study as well as from the subchronic (90-day) rat feeding study and chronic feeding studies in the dog (1-year), rat (24-month), and mouse (18-month) studies, indicate that imazapyr is not associated with any treatment-related estrogenic or endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure.* The tolerance expression established by the EPA for monitoring in plant and animal commodities is imazapyr parent only. Parent is the primary residue in crops. In animal commodities, parent is the primary residue in ruminants, and the hen metabolism study suggested that orally administered imazapyr was rapidly eliminated as unchanged parent compound. Parent imazapyr is also the established relevant residue for dietary risk assessment in plant commodities. In animal commodities, the relevant residue for risk assessment is parent imazapyr as well.

Exposure assessments were conducted to evaluate the potential risk due to chronic dietary exposure of the U.S. population and all sub-populations. The assessments were performed with DEEM-FCID version 4.02 with consumption data from the 2005-2010 NHANES surveys. For purposes of comparison, assessments were also carried out using CARES NG Food Model version 1.2.0 which uses the same consumption data as DEEM 4.02.

i. *Food.*

a. Acute Dietary Exposure. An acute dietary risk assessment is not required because no acute toxicological endpoint was identified by the EPA for imazapyr.

b. Chronic Dietary Exposure.
The proposed endpoint for use in the chronic dietary assessment is shown below.

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 = 250 mg/kg/d	UF = 100 FQPA SF = 1x	Chronic RfD = 2.5 mg/kg/d cPAD = 2.5 mg/kg/d	1-Year Dog (feeding) study

A Tier 1 assessment of potential chronic dietary exposure included the current tolerances as listed in 40 CFR 180.500 on lentil, rapeseed subgroup 20A, soybean, sunflower subgroup 20B, grass hay and forage, field corn commodities, fish, shellfish, tissues of cattle, sheep, goats, and horses, and milk. Drinking water was also included (see below). For this Tier 1 analysis, tolerance values were used for rice at 0.06 mg/kg; rice bran at 0.2 mg/kg; soybean at 4.0 mg/kg; rapeseed subgroup at 0.05 mg/kg; sunflower subgroup at 0.05 mg/kg; lentils at 0.2 mg/kg; corn grain at 0.05 mg/kg; fish at 1.0 mg/kg; shellfish at 0.1 mg/kg; kidney of cattle, sheep, goats, and horses at 0.2 mg/kg; liver, meat, fat and other meat byproducts of cattle, sheep, goats, and horses at 0.05 mg/kg; and milk at 0.01 mg/kg.

ii. *Drinking water*. Drinking water residues were included in the dietary assessment at an estimated drinking water concentration (EDWC) of 79 µg/L, which is the maximum level estimated by EPA EFED in Tier 1 drinking water modeling conducted for the imazapyr RED.

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 2.5 mg/ kg b.w./day. Results of the chronic dietary analyses for all population subgroups examined were at or below 0.7% of the cPAD. Exposure estimates for non-nursing infants, the most highly exposed subpopulation, were only 0.016612 mg/kg b.w./day (or 0.7% 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 imazapyr.

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

Population Subgroups	Exposure Estimate (mg/kg bw/day)	% cPAD
U.S. Population	0.004231	0.2
All Infants (< 1 year old)	0.012503	0.5

Children (1-2 years old)	0.011251	0.5
Children (3-5 years old)	0.007812	0.3
Children (6-12 years old)	0.005065	0.2
Youth (13-19 years old)	0.003293	0.1
Adults (20-49 years old)	0.003714	0.1
Adults (50+ years old)	0.003443	0.1
Females (13-49 years old)	0.003593	0.1

Results for imazapyr chronic dietary exposure (food and water) considering all current, pending, and proposed tolerances using CARES NG Food Model

Population Subgroups	Exposure Estimate (mg/kg bw/day)	% cPAD
U.S. Population	0.004231	0.17
All Infants (< 1 year old)	0.012505	0.5
Children (1-2 years old)	0.011251	0.45
Children (3-5 years old)	0.007812	0.31
Children (6-12 years old)	0.005065	0.2
Youth (13-19 years old)	0.003296	0.13
Adults (20-49 years old)	0.003714	0.15
Adults (50+ years old)	0.003444	0.14
Females (13-49 years old)	0.003593	0.14

2. *Non-dietary exposure*. A non-dietary exposure assessment was conducted and this assessment included the updated chronic dietary exposure values for rice tolerances. The incidental oral, dermal, and inhalation exposures were obtained from the EPA risk assessments conducted in 2005. The level of concern (LOC) for the margin of exposure (MOE) is 100 for this risk assessment. Short and intermediate-term residential aggregate MOE's are 403 for toddlers (children 1-2 years old), 713 for adult females, and 712 for the U.S. population. These MOE's demonstrate that the proposed import tolerance for rice will result in aggregate exposures with reasonable certainty of no harm.

D. Cumulative Effects.

Imazapyr 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

imazapyr 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 imazapyr from the existing uses and proposed import tolerance.

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 imazapyr from the existing uses and proposed import tolerance.

F. International Tolerances

There are no Codex tolerances established for imazapyr on rice, brown rice or polished rice.