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TEMPLATE:

[BASF]

[PP- pending]

EPA has received a pesticide petition ([PP-pending]) from [BASF Corporation],[26 Davis Drive, P.O. Box 13528, Research Triangle Park, NC 27709 (EPA Company Number 7969)] 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

(Options (pick one)

1. by establishing a tolerance for residues of

[3-(4,5-Dihydro-isoxazol-3-yl)-4-methanesulfonyl-2-methylphenyl]-(5-hydroxyl-1-methyl-1H-pyrazol-4-yl) methanone in or on the raw agricultural commodity [cottonseed, subgroup 20C] at [0.03] parts per million (ppm) and [cotton, gin byproducts] at [0.9] 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 topramezone has been determined in HPPD-resistant cotton following a preemergent application of 0.089 lb. ai/acre followed by a foliar over-the-top application of 0.045 lb. ai/acre at BBCH 60, 142 days prior to harvest; as well as in flax following an early post-emergent application of 0.011 lb. ai/acre. The metabolism in both oilseeds was similar to that observed in corn. No unique metabolism was observed in the HPPD-resistant cotton. Topramezone was found mostly unmetabolized in cotton matrices. In the cotton metabolism study, the metabolite

M670H05 was observed in small amounts in the leaves, empty capsules, and the rest of the plants. M670H05 was not observed in the cotton seed. In flax, topramezone was observed in straw and empty capsules, but not in the seed. M670H05 was observed only in the flax straw.

The metabolism of topramezone has also been determined in corn forage, stover and grain using ^{14}C labeled materials applied to young corn plants at an exaggerated application rate of 0.134 lb ai/acre. Topramezone and one significant metabolite, M670H05, were found in low levels in the plant matrices with the majority of the radioactive residues incorporated into natural products. M670H05 resulted from oxidation of the carbonyl bridge to a carboxylic acid with concomitant loss and breakdown of the pyrazole ring. The significant metabolite M670H05 was found in the rat metabolism study.

No change in the residue of concern is proposed with the addition of cotton.]

2. *Analytical method.* [The current residue of concern for topramezone is parent only; nevertheless, cottonseed, gin by-products and the processed commodities were analyzed for both parent and the metabolite M670H05. Suitable independently validated analytical methods (for animal matrices) are submitted for detecting and measuring topramezone levels in or on food with a limit of detection that is satisfactory for enforcing the requested tolerances. Residues are first extracted from the matrices by aqueous solvent then cleaned up by acid partitioning into organic solvent, then base partitioned, and quantified with application to high performance liquid chromatography with dual mass selective detectors (LC/MS/MS).]

3. *Magnitude of residues.* [A total of twelve (12) cotton residue trials were conducted in NAFTA growing regions 2, 4, 6, 8 and 10. There were two treated plots in the residue study. Topramezone in the form of BAS 670 HT Herbicide (EPA File Symbol 7969-NEW; 2.8 pounds topramezone free acid per gallon) was applied to treated plot TRT1 in 2 equal applications of 0.022 lb. ai/A (25 g ai/ha) at approximately BBCH 13 followed by a second application 14 days later prior to BBCH 61(beginning of flowering) or one application to treated plot TRT2 of 0.045 lb. ai/A (50 g ai/ha) prior to BBCH 61. Cotton was harvested at earliest commercial harvest, at least 70 days after the last application.

All samples were analyzed for residues of topramezone (BAS 670 H), and its metabolite, M670H05, using BASF Method R0096/01, which quantifies residues by LC-MS/MS. Mean recoveries for all analytes were within the acceptable range of 70-120%. Fortification levels for each analyte were adequate to bracket residue levels found in treated samples. The method limit of detection (LOD) and limit of quantitation (LOQ) for both analytes were 0.002 and 0.01 ppm, respectively in both cotton seed and gin by-products.

No residues above the LOD of topramezone or its metabolite were found in any of the untreated cottonseed samples (n=12) or cotton gin by-products samples (n=4). After two broadcast applications of topramezone (TRT1), totaling 0.045 lb ai/A per season in

cotton, maximum residues were 0.023 ppm for topramezone cottonseed samples, and 0.41 ppm for cotton gin by-products harvested at crop maturity. After 1 broadcast application of topramezone (TRT2) maximum residues, maximum residues were 0.017 ppm in cottonseed samples and 0.33 ppm in cotton gin-byproducts. Residues of M670H05 were <0.01 ppm in all samples from both treated plots.

Processing fractions: A total of 3 cotton trials were performed with two treated plots at 0.134 lb. ai/acre and 0.223 lb. ai/acre, representing a 3X or 5X rate relative to the proposed maximum label rate to determine the extent of topramezone movement into processed commodities. Cottonseed was collected from the untreated plot and the surviving plot with the highest treated application from each trial. Samples were collected from the 5X plots in two trials and the 3X plot in one trial. In all trials the residues of topramezone were <0.01 ppm in the treated cottonseed samples; nevertheless, the samples were processed into hulls, meal crude oil and refined oil. Samples were analyzed for topramezone and the metabolite M670H05. Residues of topramezone and M670H05 were <0.01 ppm in all processed commodities. There was no concentration of topramezone or its metabolite into any processed commodity.]

B. Toxicological Profile

[The toxicology database for Topramezone is current and complete. Toxicology data for Topramezone Technical has been previously reviewed and accepted by EPA. In the 2020 Draft Human Health Risk Assessment in Support of Registration Review for Topramezone (DP No. D458451), EPA determined that the rat is not a relevant model for the human health risk assessment and endpoints were selected from repeated dose studies available in mice and dogs. While all toxicology studies are discussed within this document, the rat toxicity studies have not been taken into consideration when determining the overall repeated dose toxicity of Topramezone.

1. *Acute toxicity.*

[

OPPTS Guideline	Study	Result	EPA Toxicity Category
870.1100	Acute oral toxicity – rat	LD_{50} = >2000 mg/kg	III
870.1200	Acute dermal toxicity – rat	LD_{50} = >2000 mg/kg	III
870.1300	Acute inhalation toxicity – rat	LC_{50} = >5.8 mg/L	IV
870.2400	Primary eye irritation – rabbit	Slightly irritating	III
870.2500	Primary dermal irritation – rabbit	Slightly irritating	III
870.2600	Dermal sensitization – guinea pig	Not a sensitizer	N/A
870.6200	Acute oral neurotoxicity – rat	NOAEL = 2000 mg/kg	N/A

]

2. *Genotoxicty.* [Topramezone was tested for its genotoxic potential in a battery of five *in vitro* or *in vivo* studies covering all required endpoints (gene mutations, chromosomal and chromosome aberrations, and DNA damage and repair). Several batches of Topramezone have been tested over time, from early laboratory produced

material to current manufacturing process material. Topramezone did not demonstrate any genotoxic effects *in vivo*. *In vitro*, either batch tested for chromosomal aberrations caused a slight, significant clastogenic effect in the presence of S-9 mix, but the *in vivo* test for the equivalent endpoint was negative. Three of the four batches tested in the bacterial reverse mutation assay were not mutagenic, but the batch with the least purity displayed a weak mutagenic effect at the highest dose in *Salmonella typhimurium* TA98 in the absence of S-9 mix, most likely caused by impurities, which are not present in the current production batch. Overall, the weight of the evidence is that Topramezone is not genotoxic.]

3. *Reproductive and developmental toxicity.* [The reproductive and developmental toxicity of Topramezone was investigated in a 2-generation rat reproduction study as well as in rat, mouse and several rabbit teratology studies (with different batches of Topramezone) and a rat developmental neurotoxicity study. There were no adverse effects on fertility of both genders and no effect on the reproductive performance of males in the 2-generation study at any dose tested. There was, however, a high litter loss in F_0 and F_1 associated with insufficient maternal care at higher dose levels with clear maternal toxicity. General parental toxicity included eye- and kidney effects, caused by elevated tyrosine levels due to HPPD (hydroxyphenylpyruvate dioxygenase) inhibition. The same organs were affected in subchronic and chronic feeding studies with rats. Pup effects were observed in the F_1 and F_2 generation including perinatal pup mortality and impaired body weight gain, the lower body weight effects were considered to lead to brain and spleen weight changes and delays in preputial separation. As observed in the parental animals, effects on eyes and kidneys were observed in the pups. Renal pelvis dilation was observed at lower doses, although there was no overt maternal toxicity, significantly elevated tyrosine levels were observed in the dams and pups. The NOAEL for fertility (F_0 and F_1, both genders) was 4,000 ppm (about 450 mg/kg b.w./day); the NOAEL for reproductive performance was 40 ppm (about 4 mg/kg body weight/day) for the F_1 females. The NOAEL for general toxicity was 4 ppm (about 0.4 mg/kg b.w./day). The NOAEL for developmental toxicity (growth and development of the offspring) was 4 ppm (about 0.4 mg/kg body weight/day) for the F_1 pups but was lower than 4 ppm for the F_2 pups due to renal pelvis dilations at all dose levels. In the reproduction and fertility effects study in mice, decreased body weight and body-weight gains during pre-mating (P and F_1 generations), cataracts and moderate lenticular degeneration of the eyes (F_2 females), and uremia and urolithiasis in parental animals occurred above the limit dose (>1,000 mg/kg/day); no adverse effects were in the offspring. No adverse effects were observed in the developmental toxicity study in mice up to the highest dose tested (1,000 mg/kg/day).

Developmental neurotoxicity was not observed at any dose in the developmental neurotoxicity study. At all dose levels, eye effects due to elevated tyrosine levels were found in dams and pups. Additionally, there were decreased body weights in the dams at the high and mid dose, but there were no indications of adverse effects on reproductive performance of the parental females. In pups of both genders, decreased pre and post weaning body weight gains and body weights were observed at the low dose level and above. This is an indicator of a retardation of the general physical development, which is considered to be responsible for a slight delay of maturation. The NOAEL for developmental neurotoxicity was 800 mg/kg b.w./day (highest dose tested). There is no

NOAEL for the eye lesions and reduced body weight gain of the pups. NOAELs for these effects were determined in prenatal development studies in rats, rabbits and mice. Although signs of neurotoxicity were observed in offspring in the developmental neurotoxicity study in rats, concern was low since clear NOAEL/LOAELs were identified, no evidence of neurotoxicity in the rest of the toxicological database, and the rat species is not considered an appropriate animal model for assessing human health risk for HPPD-inhibitors.

No developmental toxicity was noted in the mouse prenatal development study. In the prenatal development study in rats no teratogenic effect was observed, but there was maternal toxicity together with skeletal variations in the pups. The same skeletal variation (i.e. supernumerary ribs) was also found in rabbit prenatal development studies. This effect is associated with the family of HPPD-inhibiting substances. In addition, several rabbits had pups with a soft tissue malformation: unilateral kidney agenesis. The NOAEL for the skeletal variations and the kidney agenesis was 0.5 mg/kg b.w./day, the NOAEL for overt maternal toxicity was 50 mg/kg b.w./day. The developmental effects in rabbits occurred at dose-levels below overt maternal toxicity, however measured tyrosine blood levels in the dams were substantially elevated at these dose levels. Elevated tyrosine levels are known to cause kidney toxicity. Although there was evidence of increased quantitative susceptibility in the rabbit development studies, concern is low because rabbits were not considered an appropriate animal model for assessing human health risk for HPPD-inhibitors, there are clear NOAEL/LOAEL values for the observed developmental and offspring effects, there was no developmental effects in mice and offspring effects were only observed at doses ≥1,000 mg/kg/day, and selected endpoints are protective of offspring effects observed in mice.]

4. *Subchronic toxicity.* [The subchronic toxicity of Topramezone was investigated in 90-day feeding studies in rats, mice and dogs, and in a 28-day dermal administration study in rats. Several supplemental short-term mechanistic studies in rats and mice were performed to elucidate the mode of action. Generally, very mild toxicity was observed in mice and dogs at high doses. In a combined neurotoxicity 90-day feeding study in rats, no signs of neurotoxicity were observed. Effects were seen in the pancreas, eye, kidney, liver and thyroid gland. The target organs are identical with those in the chronic feeding studies with rats. Two modes of action have been elucidated for Topramezone by short-term mechanistic studies, one leading to effects on eyes, kidney and liver, and a second leading to effects at the thyroid: Topramezone causes elevated tyrosine levels by HPPD-inhibition accounting for effects on eye, liver and kidney. The mouse is the accepted model for this tyrosine level elevations, and a NOAEL of 1.2 mg/kg b.w./day was established for tyrosine elevation in mice. Other mechanistic studies demonstrated an impairment of pituitary-thyroid hormone levels by enhancing the hepatic clearance of thyroid hormones. The NOAEL for interference with thyroid hormones was 0.4 mg/kg b.w./day. The NOAEL for effects on the exocrine pancreas in rats was 1.1 mg/kg b.w./day. Similar effects were seen in the 28-day dermal study with rats; the NOAEL was 100 mg/kg b.w./day. There were no effects observed in relevant species (mice and dogs) at doses relevant for risk assessment to establish an incidental oral endpoint. Adverse effects were observed in the subchronic toxicity study in dogs and the reproduction and fertility effects study in mice, but only at doses >1,000 mg/kg/day (the limit dose). There was no increased susceptibility observed in the mouse developmental or reproduction toxicity studies for topramezone.]

5. *Chronic toxicity.* [The chronic toxicity and oncogenicity studies with Topramezone include two 12-month feeding studies with dogs, an 18-month mouse feeding study, a 12-month rat chronic feeding study and a 24-month rat oncogenicity study. In the chronic feeding studies in rats the main target organs were eye, liver, kidney, thyroid gland and pancreas. The same organs were affected in the subchronic studies. Short-term mechanistic studies demonstrated that Topramezone causes elevated tyrosine levels by HPPD-inhibition accounting for effects on eye, liver and kidney. The mouse is the accepted model for this tyrosine level elevation, and a NOAEL of 1.2 mg/kg b.w./day was established for tyrosine elevation in mice. The NOAEL for effects on the exocrine pancreas in rats 6 ppm in both genders (0.4 and 0.5 mg/kg b.w./day in males and females respectively). At the end of the 24-month oncogenicity study, there was a slight but significant increase in benign thyroid adenomas in both genders. The thyroid was the only organ affected and the increase of the adenomas was significant only at the highest dose tested, while considerable general toxicity was already seen at 20-times lower doses. The mechanism of thyroid tumor formation by Topramezone was thoroughly investigated in short-term mechanistic studies. An enhanced hepatic clearance of thyroid hormones impairs pituitary-thyroid hormone levels leading to hypertrophy, hyperplasia and ultimately neoplasia. There is general agreement that this mechanism is well-understood in rodents and is of minor relevance to humans. A clear NOAEL of 0.4 mg/kg b.w./day was demonstrated for effects on thyroid hormone levels. A threshold (non-linear) cancer assessment is proposed and a cancer classification as "not likely to be a human carcinogen".

In the 18-month chronic feeding study in mice increased liver weights were seen at high doses. The NOAEL was 80 ppm (19 and 26 mg/kg b.w./day in males and females respectively). Topramezone was not carcinogenic to mice. In the chronic dog study mild reductions of the body weight were observed at high doses. The NOAEL was 100 ppm (2.9 and 3.1 mg/kg b.w./day in males and females respectively). Following chronic exposure, hemorrhaging of the urinary bladder wall were observed in males at 248 mg/kg/day. No effects were observed in females after subchronic and chronic exposure.]

6. *Animal metabolism.* [In the rat metabolism studies the majority of the residue was excreted within 48 hours from both males and females. In all matrices investigated unchanged parent is the main component. Degradation starts with hydroxylation of the oxazole ring. The identified metabolites from both pyrazole ring label and phenyl ring label studies are reported. Goat and hen metabolism studies were conducted with feeding levels of about 10 ppm. In the goat, the majority of the applied dose was excreted. Non-metabolized BAS 670 H (i.e., Topramezone parent) was the major radioactive residue, and M670H02, formed from hydroxylation at the 4-position of the isoxazole ring, was the only significant metabolite formed. In poultry, BAS 670 H was also rapidly excreted. Residues in liver consisted mainly of BAS 670 H and the only significant metabolite in poultry was again M670H02. The significant metabolite M670H02 was found in the rat metabolism study.]

7. *Metabolite toxicology.* [The toxicity of the metabolites of Topramezone with potential exposure to humans was concurrently evaluated during toxicity testing of the parent because both plant and animal metabolites are formed during the course of

toxicity testing. Both plant and animal metabolites are considered not of toxicological concern. Some testing was conducted on the anaerobic aquatic metabolite, 670M10. The results as given below show no toxicological concern:

OPPTS Guideline	Study	Result
870.5100	Bacterial reverse mutation test (Ames)	Negative
870.5300	Mammalian somatic cell gene mutation test (MNT)	Negative
870.5395	Cytogenetic study *in vivo* (mouse – HPRT)	Negative
NA	28-Day feeding – rat	NOAEL = M: 1197 mg/kg F: 1304 mg/kg

]

8. *Endocrine disruption*. [Topramezone has been shown to alter thyroid hormone levels in rats as also observed with other 4-hydroxyphenylpyruvate dioxygenase (HPPD) enzyme inhibitor active ingredients. However, there have been no effects noted on sexual or other hormones in numerous subchronic and chronic toxicity studies with multiple species.]

C. Aggregate Exposure

1. *Dietary exposure.* [Exposure assessments were conducted to evaluate the potential risk due to chronic dietary exposure of the U.S. population to residues of Topramezone. The current tolerance values are listed in the U.S. 40 CFR § 180.612. This analysis includes all commodities with established tolerances values and proposed new tolerance for cottonseed = 0.03 ppm.]

i. *Food.*

[Acute Dietary Exposure Assessment: An acute endpoint has not been established; therefore, no acute dietary assessment has been performed.

Chronic Dietary Exposure Assessment: A chronic dietary exposure (food and drinking water) assessment was conducted using the currently established tolerances for Topramezone (40 CFR § 180.612) and the proposed tolerance for cottonseed (0.03 ppm). The assessment was conducted using tolerance values, default process factors, and 100% crop treatment factors. The consumption data was from the NHANES 2-day food consumption data for 2005-2010 and the EPA Food Commodity Ingredient Database (FCID). Assessments were compared using Exponent's Dietary Exposure Evaluation Module (DEEM-FCID) software (ver. 4.02) and CARES NG Dietary Model (Ver. 1.2.4). The water concentration used in the chronic dietary assessment was 45 ppb based on the aquatic application rate and not does not consider degradation in the water body.

The chronic Population Adjusted Dose (cPAD) used for U.S. population and all sub-populations is 0.81 mg/kg bw/day. This endpoint is based on the NOAEL value of 81 mg/kg/day using the standard inter- and intra-species uncertainty factors of 100X and with a FQPA safety factor of 1. The most highly exposed population sub-group was

infants (<1year old) which utilized 0.43 % cPAD in both models. The results of the chronic dietary assessment are presented in the table below.

Population	DEEM - V 4.02		CARES NG - V 1.2.4	
	Exposure (mg a.i./kg-bw/day)	% cpad	Exposure (mg a.i./kg-bw/day)	% cpad
Total US Population	0.000962	0.12	0.000961	0.12
Infants < 1 yr	**0.003450**	**0.43**	**0.003451**	**0.43**
Children 1-2 yrs	0.001372	0.17	0.001372	0.17
Children 3-5 yrs	0.001130	0.14	0.001131	0.14
Children 6-12 yrs	0.000837	0.10	0.000839	0.10
Youth 13-19 yrs	0.000687	0.08	0.000688	0.08
Adults 20-49 yrs	0.000949	0.12	0.000948	0.12
Adults 50+ yrs	0.000919	0.11	0.000918	0.11
Female 13-49 yrs	0.000928	0.11	0.000928	0.11

The results of the analysis show that for all populations, the exposures are below the US EPA level of concern (< 100% cPAD) using both models. Additional refinements in the chronic dietary risk assessment (i.e. utilizing anticipated residue values and percent crop treated values) would further reduce the estimated exposure values

Acute Aggregate Exposure and Risk (food and water): No acute endpoint has been established.

Chronic Aggregate Exposure and Risk (food and water): The aggregate chronic risk includes exposure of Topramezone from food and water (see table above). The results demonstrate there are no risk concerns for any subpopulation based on the proposed uses and the results meet the FQPA standard of reasonable certainty of no harm.]

ii. Drinking water. [The concentration of Topramezone in water is based on the aquatic use pattern with an application rate of 45 ppb. The chronic surface water concentration used in the assessment was also 45 ppb, which assumes no degradation in the water body. This is a very conservative water value and over-estimates the actual chronic drinking water exposure.]

2. *Non-dietary exposure.* [Topramezone is registered for use on corn (field, pop, sweet and seed) and sugarcane, as well as aquatic vegetation, non-crop ornamentals, African marigolds, residential turf grass, rights-of-way, tree plantations, and other non-crop areas. As part of the 2020 Registration Review of Topramezone, EPA revised their risk assessment for uses on golf courses, sod farms, and residential turfgrass, lowering the dermal absorption value from 13% to 2.6% (DP No. D388807). For Topramezone, only potential chronic exposures from food and drinking water were aggregated since PODs were not selected for the residential pathways of exposure and acute dietary. Since no residential uses are being added to the label and there are no post-application risks of concern, no residential scenarios were quantitatively conducted and considered for use in the aggregate.]

D. Cumulative Effects [At this time, Topramezone has not been included in the HPPD cumulative assessment group (CAG) due to its low hazard potential for common mechanism endpoints. Therefore, there is no reason to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action EPA has not assumed that Topramezone has a common mechanism of toxicity with other substances.]

E. Safety Determination

1. *U.S. population.* [Based on the current risk assessments EPA can conclude that there is a reasonable certainty that no harm will result to the general population from aggregate exposures to topramezone residues from the proposed uses.]

2. *Infants and children*. [Based on the current risk assessments, EPA can conclude that there is a reasonable certainty that no harm will result to infants and children from aggregate exposures to topramezone residues from the proposed uses.]

F. International Tolerances [No maximum residue levels (MRLs) have been established for Topramezone by the Codex Alimentarius Commission (CODEX) or in Mexico. Canada has established tolerances in field corn (0.01 ppm), sweet corn kernels plus cob with husk removed (0.01 ppm) and oilseed Crop Subgroup 20A (0.01 ppm), and there is currently a default tolerance of 0.1 ppm in cottonseed.]