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TEMPLATE:

BASF

PP#3F9075

EPA has received a pesticide petition (3F9075) from BASF Corporation, 26 Davis Drive, P.O. Box 13528, Research Triangle Park, NC 27709 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 tolerances from direct use in corn/sweet corn for residues of boscalid, 3-pyridinecarboxamide,2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on the raw commodity corn, field, forage at 20 ppm (parts per million), corn, sweet, forage at 20 ppm (parts per million), corn, pop, forage at 20 ppm (parts per million), corn, field, stover at 50 ppm (parts per million) corn, sweet, stover at 50 ppm (parts per million), corn, pop, stover at 50 ppm (parts per million), Cereal Grain, Field Corn Subgroup 15-22C at 0.2 ppm (parts per million), and Cereal Grain, Sweet Corn Subgroup 15-22D at 0.2 ppm (parts per million). In addition, the petition includes the request to modify the expression of the existing tolerances for indirect or inadvertent residues of boscalid, 3-pyridinecarboxamide,2-chloro-N-(4'-chloro[1,1'-biphenyl]-2-yl), in or on grain, cereal, group 15 at 0.2 ppm to grain, cereal, group 15, except corn at 0.2 ppm (parts per million), Grain, cereal, forage, fodder and straw, group 16, forage at 2.0 ppm (parts per million) to Grain, cereal, forage, fodder and straw, group 16, forage, except corn forage at 2.0 ppm (parts per million) and Grain, cereal, forage, fodder and straw, group 16, stover at 1.5 ppm (parts per million) to Grain, cereal, forage, fodder and straw, group 16, stover, except corn stover at 1.5 ppm (parts per million). 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.* Nature of the residue studies (OPPTS Harmonized Guideline 860.1300) were conducted in grapes, lettuce and beans as representative crops in order to characterize the fate of boscalid (BAS 510 F) in all crop matrices. In all three crops the boscalid (BAS 510 F) Residues of Concern (ROC) were characterized as parent boscalid (BAS 510 F). A confined rotational crop study also determined that parent was the residue of concern in the representative crops of radish, lettuce and wheat.

2. *Analytical method.* In plants, using method D9908 residues of boscalid (BAS 510 F) were extracted from plant commodities, with methanol (MeOH): water: 2 N

HCl (70:25:5; v/v/v) and centrifuged. Residues from each commodity were then diluted with 1N HCl saturated with NaCl and partitioned into cyclohexane. Residues were concentrated to dryness, re-dissolved in MeOH: water: 4 mM ammonium formate (80:20:0.1, v/v/v), and analyzed using LC/MS/MS using the m/z 343→307 ion transition to detect and quantify boscalid. Residues are quantified using an external calibration curve of boscalid standards. The validated level of quantitation (LOQ) (LLMV, lower limit of method validation) was 0.05 ppm.

3. *Magnitude of residues.* Field trials were carried out in order to determine the magnitude of the residue of boscalid (BAS 510F) in corn to satisfy the requirements for a tolerance of boscalid in corn. The number and locations of field trials are in accordance with the OPPTS Guideline 860.1500. Field trials were carried out using the maximum use rate, the maximum number of applications, and the minimum pre-harvest interval.

B. Toxicological Profile

1. *Acute toxicity.* Based on available acute toxicity data, boscalid and its formulated products do not pose acute toxicity risks. The acute toxicity studies place technical boscalid (BAS 510 F) in toxicity category IV for acute oral; category III for acute dermal and category IV for acute inhalation. Boscalid is category IV for both eye and skin irritation and it is not a dermal sensitizer. An acute neurotoxicity study in rats was conducted up to 2000 mg/kg bw/day with no evidence of neurotoxicity. For the use on corn, the proposed product is Endura® Fungicide (BAS 510 02/04 F) containing boscalid (BAS 510F) as the active ingredient. Endura® Fungicide (BAS 510 02/04 F) has an acute oral toxicity category of III, acute dermal of category IV, acute inhalation of category IV, eye irritation of category IV, skin irritation of category III, and is not a dermal sensitizer.

2. *Genotoxicity.* Ames Test (1 Study; gene point mutation): Negative; In Vitro CHO/HGPRT Locus Mammalian Cell Mutation Assay (1 Study; point gene mutation): Negative; In Vitro V79 Cell Cytogenetic Assay (1 Study; Chromosome Damage): Negative; In Vivo Mouse Micronucleus (1 Study; Chromosome Damage): Negative; In Vitro Rat Hepatocyte (1 Study; DNA damage and repair): Negative. Boscalid has been tested in a total of five genetic toxicology assays consisting of in vitro and in vivo studies. Boscalid did not show any mutagenic, clastogenic or other genotoxic activity when tested under the conditions of the studies mentioned above. Therefore, boscalid does not pose a genotoxic hazard to humans.

3. *Reproductive and developmental toxicity.* The potential reproductive and developmental toxicity of boscalid was investigated in a two-generation rat reproduction study, as well as in rat and rabbit teratology studies. There were no adverse effects on reproduction in the two-generation study at any dose tested. The reproductive NOAEL is 10,000 ppm (1165 and 1181 mg/kg bw/day for males and females, respectively), the highest dose tested. Toxicity to the offspring was seen at 1,000 ppm in the form of decreased pup weights in the F2 males, and at 10,000 ppm in the form of decreased pup weights for both males and females of both the F1 and F2 generations. The offspring NOAEL is 100 and 1000 ppm (11 and 116 mg/kg bw/day) for males and females, respectively. In males of the F1 generation, reduced body weight and reduced body

weight gain were observed at 10,000 ppm. Additionally, hepatocyte degeneration was observed in male animals of both the F0 and F1 generations at 10,000 ppm. The parental systemic NOAEL is 1000 and 10,000 (113 and 1181 mg/kg bw/day) for males and females, respectively.

No teratogenic effects were noted in either the rat or rabbit developmental studies. In the rat study, evidence of maternal or developmental toxicity was not observed at any dose (highest dose tested of 1,000 mg/kg bw/day). In the rabbit teratology study, at the high dose of 1,000 mg/kg bw/day, a maternal body weight gain decrease compared to controls of 81% was observed during the treatment period. Reduced food consumption, reduced body weight and abortions in three dams, were also seen at 1,000 mg/kg bw/day. The NOAEL for both maternal and developmental toxicity was determined to be 300 mg/kg bw/day.

Neurotoxicity was not observed at any dose in the developmental neurotoxicity study. Reduced pup body weights were observed at the high and mid dose levels of 1000 and 10,000 ppm (118 and 1,183 mg/kg bw/day, respectively). No developmental toxicity was seen at the low dose of 14 mg/kg bw/day (100 ppm). Although no maternal toxicity was seen in this study, other studies which evaluated more parameters at similar doses of boscalid demonstrated maternal toxicity.

The Agency concluded that there are no residual uncertainties for pre- and postnatal toxicity, as the degree of concern is low for the susceptibility seen in the above studies, and the dose and endpoints selected for the overall risk assessments will address the concerns for the body weight effects seen in the offspring. Although the dose selected for overall risk assessments (21.8 mg/kg bw/day) is higher than the NOAELs in the 2-generation reproduction study (11 mg/kg bw/day) and the developmental neurotoxicity study (14 mg/kg bw/day), these differences are considered to be an artifact of the dose selection process in these studies. For example, there is a 10-fold difference between the LOAEL (113 mg/kg bw/day) and the NOAEL (11 mg/kg bw/day) in the two-generation reproduction study. A similar pattern was seen with regard to the developmental neurotoxicity study, where there is also a 10-fold difference between the LOAEL (147 mg/kg bw/day) and the NOAEL (14 mg/kg bw/day). There is only a 2-3-fold difference between the LOAEL (57 mg/kg bw/day) and the NOAEL (21.8 mg/kg bw/day) in the critical chronic dog study which was used for risk assessment. Because the gap between the NOAEL and LOAEL in the 2-generation reproduction and developmental neurotoxicity studies was large and the effects at the LOAELs were minimal, the true no-observed-adverse-effect-level was probably considerably higher. Therefore, the selection of the NOAEL of 21.8 mg/kg bw/day from the 1-year dog study is conservative and appropriate for the overall risk assessments. In addition, the endpoints for risk assessment are based on thyroid effects seen in multiple species (mice, rats and dogs) and after various exposure durations (subchronic and chronic exposures) which were not observed at the LOAELs in either the 2-generation reproduction or the developmental neurotoxicity studies. Based on these data, the Agency concluded that there are no residual uncertainties for pre- and post-natal toxicity.

4. *Subchronic toxicity.* The subchronic toxicity of boscalid was investigated in 90–day feeding studies with rats, mice and dogs, and in a 28–day dermal administration study

in rats. Additionally, a 90–day neurotoxicity study in rats was performed. Generally, mild toxicity was observed including alterations in various clinical chemistry parameters and effects on the liver and thyroid. In the rat, effects observed were increased thyroid weight and increased incidence of thyroid hyperplasia, as well as follicular epithelial hypertrophy. Increased liver weights and an increased incidence of marked fatty changes in the liver were observed in mice. Changes observed in dogs were increased serum alkaline phosphatase and liver weights. The lowest subchronic toxicity NOAEL was from the dog study (7.6 and 8.1 mg/kg bw/day in males and females, respectively).

No evidence of immunotoxicity was observed in a 28-day immunotoxicity study in rats. In the 28–day repeat dose dermal study, no systemic effects were noted up to the highest dose tested of 1,000 mg/kg bw/day.

In a 90–day rat neurotoxicity study, no signs of neurotoxicity were observed in the pups or adults. The NOAEL is the highest tested of 15,000 ppm (1,050 and 1,272 mg/kg bw/day in males and females, respectively).

5. *Chronic toxicity.* The chronic toxicity/oncogenicity studies with boscalid include a 12–month feeding study with Beagle dogs, an 18–month B63CF1 mouse feeding study, a 24–month Wistar rat chronic feeding study and a 24–month Wistar rat oncogenicity study. At the highest dose tested in dogs, effects observed consisted primarily of increased liver and thyroid weights and some serum clinical chemistry changes. The NOAEL was 800 ppm (21.8 mg/kg bw/day males; 22.1 mg/kg bw/day females).

In the mouse oncogenicity study, decreased body weights were seen in males at 2000 ppm (331 mg/kg bw/day) and in both males and females at 8000 ppm (1345 and 1804 mg/kg bw/day for males and females, respectively). Also, in males at 8000 ppm, increased liver weights and an increased incidence of peripheral hypertrophy of the liver were observed. The NOAEL was 400 ppm and 2000 ppm (65 and 443 mg/kg bw/day) for male and female mice, respectively.

In both the rat chronic and oncogenicity studies, the highest dose tested of 15,000 ppm exceeded a maximum tolerated dose (MTD) and was discontinued after 17 months. Effects observed at the next highest dose of 2,500 ppm (110 and 150 mg/kg bw/day for males and females, respectively) were increased thyroid weights and histopathological changes in the thyroid which included follicular cell hypertrophy, hyperplasia and adenomas. The NOAEL was 500 ppm (22 and 30 mg/kg bw/day for male and female rats, respectively).

No evidence of treatment-induced oncogenicity was observed in the mouse study. In the rat, a slight increase in thyroid follicular cell adenomas was seen in both sexes at the high dose when the data from both chronic and oncogenicity bioassays are combined. A non-genotoxic (threshold) mode of action (MOA) for the thyroid follicular cell adenomas was demonstrated from results of several studies.

Based on review of the available data, the Reference Dose (RfD) for boscalid was based on a 1-year feeding study in dogs with a NOAEL of 21.8 mg/kg bw/day. Using an uncertainty factor of 100, the RfD is calculated to be 0.218 mg/kg bw/day. Based on the acute toxicity data, an acute dietary risk assessment is not needed.

Boscalid was shown to be non-carcinogenic in mice. There was a slight increase in thyroid follicular cell adenomas at the high dose in both sexes in the rat. A non-genotoxic (threshold) MOA was demonstrated for the thyroid tumors. The Agency concluded a carcinogenicity classification of "suggestive evidence of carcinogenicity" and that a dose response assessment for cancer was not needed.

6. *Animal metabolism.* In the rat, the predominant route of excretion of boscalid (BAS 510F) is fecal with urinary excretion being minor. The half-life of boscalid is less than 24 hours. Saturation of absorption appears to be occurring at the high dose level. Boscalid is rapidly and intensively metabolized to a large number of biotransformation products. The hydroxylation of the diphenyl moiety was quantitatively the most important pathway. Second most important pathway was the Cl substitution in the 2-chloropyridine ring by SH due to coupling with glutathione. No major differences were observed. In hens and goats, the residues of concern were determined to be parent, the hydroxylated metabolite M510 F01 (2-chloro-N-(4'chloro-5-hydroxy- biphenyl-2-yl)nicotinamide), and the glucuronic acid metabolite M510 F02.

7. *Metabolite toxicology*. No additional studies were required for metabolite toxicology.

8. *Endocrine disruption*. No specific tests have been conducted with boscalid to determine whether the chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. However, there were no significant findings in other relevant toxicity studies (i.e., subchronic and chronic toxicity, teratology and multi-generation reproductive studies) which would suggest that boscalid produces endocrine related effects.

C. Aggregate Exposure

1. *Dietary exposure.* The last assessment conducted to evaluate the potential risk due to chronic dietary exposure of the U.S. population and sub-populations to residues of boscalid was McGovern, R., Boscalid. Human Health Risk Assessment for the Establishment of a Permanent Tolerance Without a U.S. Registration on Tea; DP Barcode: D459618; 4/01/2021. This analysis included all crops with established boscalid tolerance values. No new proposed tolerances listed in first section of this document affect the dietary exposure. Tolerance values for boscalid have previously been established and are listed in U.S. 40 CFR § 180.589.

i. Food.

Acute Dietary Exposure Assessment

There is no acute population adjusted dose (aPAD) or acute reference dose (aRfD) for boscalid, so an acute dietary exposure assessment was not conducted.

Chronic Dietary Exposure Assessment

The chronic population adjusted dose (cPAD) of 0.218 mg/kg bw/day, as per the Federal Register Vol. 78, No. 217, was used to characterize risk associated with chronic dietary

exposures. The EPA in McGovern, R., Boscalid. Human Health Risk Assessment for the Establishment of a Permanent Tolerance Without a U.S. Registration on Tea; DP Barcode: D456100; 4/01/2021 conducted an unrefined chronic dietary exposure and risk assessment incorporating tolerance-level residues, 100% PCT, empirical and default processing factors, and anticipated secondary residues in livestock calculated from dietary burden. The dietary feed burden did not change from the previous dietary feed burden for diet roughage for livestock established in Tsaur, N; Boscalid. Human Health Risk Assessment for Proposed Use on Alfalfa and Citrus (Crop Group 10), and for Proposed Increase in Tolerance on Stone Fruits (Crop Group 12)DP# 364447, DP Barcode: 363305 1/6/2010 which is driven by grass and alfalfa RACs in the roughage category. The EPA concluded the available cattle and poultry feeding studies are adequate and cover the potential levels of dietary exposure of livestock to boscalid residues.

The risk estimate for the general U.S. population is 24% of the cPAD, and the risk estimate for children (1-2 years old; the most highly exposed population subgroup) is 57% of the cPAD. The EPA conclusion was these risks are not of concern.

The results of the DEEM model (D459618; 4/01/2021)

Table 1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Boscalid DP Barcode: D459618

Population Subgroup	Acute Dietary		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	%aPAD	Dietary Exposure (mg/kg/day)	%cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	NA		0.052132	24	NA	
All Infants (<1 year old)			0.078916	36		
Children 1-2 years old			**0.123941**	**57**		
Children 3-5 years old			0.095934	44		
Children 6-12 years old			0.054516	25		
Youth 13-19 years old			0.038693	18		
Adults 20-49 years old			0.047997	22		
Adults 50+ years old			0.047693	22		
Females 13-49 years old			0.049155	23		

ii. *Drinking water.* The drinking water concentrations were determined using PRZM-GW and FIRST models for all uses (DP Barcode: D459618). The use resulting in the highest estimated concentrations is the turf grass use. EFED recommends the average value of 436 ug/L for the chronic and cancer assessment. This estimated drinking water concentration was included in the dietary exposure modeling.

Acute Aggregate Exposure and Risk (food and water)

Since the U.S. EPA Toxicological Endpoint Selection (TES) Committee has evaluated the boscalid toxicity data and determined there was no toxicological endpoints for acute dietary exposure, the determination of an acute aggregate exposure and risk evaluation was not required.

Short and Intermediate-Term Aggregate Exposure and Risk (food, water, and residential)
Short-term aggregate exposure considers residential exposure plus chronic exposure from food and water. Residential exposure is used to refer to non-occupational and non-dietary exposure. No new residential uses are currently being registered for boscalid that would increase non-dietary exposure. The boscalid residential exposure values used in this risk assessment were previously determined by the EPA (April 1, 2021). The exposure assessment was conducted using the updated 2012 Residential SOP's along with policy changes for body weight assumptions. The margins of exposure are presented in Table 2.

Table 2. Estimated Short/Intermediate Term Aggregate Exposure and Risk of Boscalid (Target MOE = 100)

Population	Oral NOAEL (mg/kg/day)	Food + Water Exposure (mg/kg/day)	Oral MOE	Dermal NOAEL (mg/kg/day)	Residential Exposure (mg/kg/day)	Dermal MOE	Total Combined MOE
Children 6-11 years old	21.8	0.054516	400	21.8	0.081	270	160
Youth 11-16 years old	21.8	0.054516	563	21.8	0.0026	8,600	390
Adult	21.8	0.052132	418	21.8	0.118	190	130

Total combined MOE = 1/[(1/MOE oral) + (1/MOE dermal)]; Target MOE = 100

The results demonstrate that the margins of exposure exceed the level of concern for any subpopulation based on established and new uses. The results clearly meet the FQPA standard of reasonable certainty of no harm.

Chronic Aggregate Exposure and Risk (food and water)
The aggregate chronic risk includes residues of boscalid from food and water (Table 1). Exposures from residential uses are not included in the chronic aggregate assessment. The results demonstrate that the margins of exposure exceed the level of concern for any subpopulation based on established and new uses. The results clearly meet the FQPA standard of reasonable certainty of no harm.

2. *Non-dietary exposure*. Boscalid is currently registered for the following uses that could result in residential (= non-dietary) exposures: Golf course turf, residential fruit and nut trees and residential ornamentals and landscape gardens.

All residential exposures are considered short-term in duration. The residential handler assessment included short-term exposures via the dermal and inhalation routes from treating residential ornamentals, landscape gardens, and trees.

In terms of post-application exposure, there is the potential for dermal post-application exposure for individuals as a result of being in an environment that has been previously treated with boscalid. Short-term dermal exposures were assessed for adults, youth 11

to 16 years old and children 6 to 11 years old. Incidental oral exposure to children 1 to 2 years old is not expected from treated golf course turf or use in residential gardens and trees.

The scenarios used in the aggregate assessment were those that resulted in the highest exposures from the different residential uses. The highest exposures for all age groups were associated with only residential post-application dermal exposures, not inhalation exposures, and consist of the following:

- The residential dermal exposure for use in the adult aggregate assessment reflects dermal exposure from post-application activities on treated gardens.
- The residential dermal exposure for use in the youth (11-16 years old) aggregate assessment reflects dermal exposure from post-application golfing on treated turf.
- The residential dermal exposure for use in the child (6-11 years old) aggregate assessment reflects dermal exposure from post-application activities in treated gardens.

D. Cumulative Effects

Boscalid is a foliar fungicide chemically belonging to the Pyridine-carboxamides class of fungicides. Boscalid acts in the fungal cell by inhibition of mitochondrial respiration through the succinate-ubiquinone oxidase reductase system (SDH Inhibitor) in Complex II of the mitochondrial electron transport chain.

Boscalid was not found to share a common mechanism of toxicity with any other substances and it does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, it is assumed that boscalid does not have a common mechanism of toxicity with other substances and therefore no assumptions regarding cumulative exposure with other compounds have been made. This is supported by the Agency's evaluation of boscalid.

E. Safety Determination

1. *U.S. population.* Using the conservative exposure assumptions described above and based on the completeness of the toxicity database, it can be concluded that dietary exposure to boscalid from all existing and proposed crop uses will be 24% of the cPAD for the overall US population. The Agency generally has no concern for exposures below 100% of the PAD because the PAD represents the level at or below which daily aggregate exposures will not pose appreciable risks to human health. Thus, it can be concluded that there is a reasonable certainty that no harm will result from aggregate exposure to residues arising from the proposed tolerances that are the subject of this petition.

2. *Infants and children*. Using the conservative exposure assumptions described above and based on the completeness of the toxicity database, it can be concluded that dietary exposure to boscalid from all existing and proposed import crop uses will be 57% of the cPAD for 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 boscalid residues.

F. International Tolerances

There is a 0.1 ppm Codex MRL for cereal grains and a 5 ppm Codex MRL for straw and hay of cereal grains (dry weight) set for boscalid.